Cochrane Library

Cochrane Database of Systematic Reviews

Dopamine agonists for preventing ovarian hyperstimulation syndrome (Review)

Tang H, Mourad SM, Wang A, Zhai SD, Hart RJ

Tang H, Mourad SM., Wang A, Zhai S-D, Hart RJ.
Dopamine agonists for preventing ovarian hyperstimulation syndrome.
Cochrane Database of Systematic Reviews 2021, Issue 4. Art. No.: CD008605.
DOI: 10.1002/14651858.CD008605.pub4.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Dopamine agonists for preventing ovarian hyperstimulation syndrome

Huilin Tang[1], Selma M. Mourad[2], Aihua Wang[3], Suo-Di Zhai[4], Roger J Hart[5]

[1]Institute for Drug Evaluation, Peking University Health Science Center, Beijing, China. [2]Radboud University Medical Centre, Nijmegen, Netherlands. [3]Department of Pharmacy, Beijing Obstetrics and Gynecology Hospital, Capital Medical University, Beijing, China. [4]Department of Pharmacy, Therapeutic Drug Monitoring and Clinical Toxicology Center of Peking University, Peking University Third Hospital, Beijing, China. [5]School of Women's and Infants' Health, The University of Western Australia, King Edward Memorial Hospital and Fertility Specialists of Western Australia, Subiaco, Perth, Australia

Contact: Huilin Tang, huiltang85@gmail.com.

Editorial group: Cochrane Gynaecology and Fertility Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 4, 2021.

Citation: Tang H, Mourad SM., Wang A, Zhai S-D, Hart RJ. Dopamine agonists for preventing ovarian hyperstimulation syndrome. *Cochrane Database of Systematic Reviews* 2021, Issue 4. Art. No.: CD008605. DOI: 10.1002/14651858.CD008605.pub4.

ABSTRACT

Background

Ovarian hyperstimulation syndrome (OHSS) is a potentially serious complication of ovarian stimulation in assisted reproduction technology (ART). It is characterised by enlarged ovaries and an acute fluid shift from the intravascular space to the third space, resulting in bloating, increased risk of venous thromboembolism, and decreased organ perfusion. Most cases are mild, but forms of moderate or severe OHSS appear in 3% to 8% of in vitro fertilisation (IVF) cycles. Dopamine agonists were introduced as a secondary prevention intervention for OHSS in women at high risk of OHSS undergoing ART treatment.

Objectives

To assess the effectiveness and safety of dopamine agonists in preventing OHSS in women at high risk of developing OHSS when undergoing ART treatment.

Search methods

We searched the following databases from inception to 4 May 2020: Cochrane Gynaecology and Fertility Specialised Register, CENTRAL, MEDLINE, Embase, CINAHL, and PsycINFO for randomised controlled trials (RCTs) assessing the effect of dopamine agonists on OHSS rates. We also handsearched reference lists and grey literature.

Selection criteria

We considered RCTs for inclusion that compared dopamine agonists with placebo/no intervention or another intervention for preventing OHSS in ART. Primary outcome measures were incidence of moderate or severe OHSS and live birth rate. Secondary outcomes were rates of clinical pregnancy, multiple pregnancy, miscarriage, and adverse events.

Data collection and analysis

Two review authors independently screened titles, abstracts, and full texts of publications; selected studies; extracted data; and assessed risk of bias. We resolved disagreements by consensus. We reported pooled results as odds ratios (OR) and 95% confidence interval (CI) by the Mantel-Haenszel method. We applied GRADE criteria to judge overall quality of the evidence.

Main results

The search identified six new RCTs, resulting in 22 included RCTs involving 3171 women at high risk of OHSS for this updated review. The dopamine agonists were cabergoline, quinagolide, and bromocriptine.

Dopamine agonists versus placebo or no intervention

Dopamine agonists probably lowered the risk of moderate or severe OHSS compared to placebo/no intervention (OR 0.32, 95% CI 0.23 to 0.44; 10 studies, 1202 participants; moderate-quality evidence). This suggests that if the risk of moderate or severe OHSS following placebo/no intervention is assumed to be 27%, the risk following dopamine agonists would be between 8% and 14%. We are uncertain of the effect of dopamine agonists on rates of live birth (OR 0.96, 95% CI 0.60 to 1.55; 3 studies, 362 participants; low-quality evidence). We are also uncertain of the effect of dopamine agonists on clinical pregnancy, multiple pregnancy, miscarriage or adverse events (very low to low-quality evidence).

Dopamine agonists plus co-intervention versus co-intervention

Dopamine agonist plus co-intervention (hydroxyethyl starch, human albumin, or withholding ovarian stimulation 'coasting') may decrease the risk of moderate or severe OHSS compared to co-intervention (OR 0.48, 95% CI 0.28 to 0.84; 4 studies, 748 participants; low-quality evidence). Dopamine agonists may improve rates of live birth (OR 1.21, 95% CI 0.81 to 1.80; 2 studies, 400 participants; low-quality evidence). Dopamine agonists may improve rates of clinical pregnancy and miscarriage, but we are uncertain if they improve rates of multiple pregnancy or adverse events (very low to low-quality evidence).

Dopamine agonists versus other active interventions

We are uncertain if cabergoline improves the risk of moderate or severe OHSS compared to human albumin (OR 0.21, 95% CI 0.12 to 0.38; 3 studies, 296 participants; very low-quality evidence), prednisolone (OR 0.27, 95% CI 0.05 to 1.33; 1 study; 150 participants; very low-quality evidence), hydroxyethyl starch (OR 2.69, 95% CI 0.48 to 15.10; 1 study, 61 participants; very low-quality evidence), coasting (OR 0.42, 95% CI 0.18 to 0.95; 3 studies, 320 participants; very low-quality evidence), calcium infusion (OR 1.83, 95% CI 0.88 to 3.81; I^2 = 81%; 2 studies, 400 participants; very low-quality evidence), or diosmin (OR 2.85, 95% CI 1.35 to 6.00; 1 study, 200 participants; very low-quality evidence). We are uncertain of the effect of dopamine agonists on rates of live birth (OR 1.08, 95% CI 0.73 to 1.59; 2 studies, 430 participants; low-quality evidence). We are uncertain of the effect of dopamine agonists on clinical pregnancy, multiple pregnancy or miscarriage (low to moderate-quality evidence). There were no adverse events reported.

Authors' conclusions

Dopamine agonists probably reduce the incidence of moderate or severe OHSS compared to placebo/no intervention, while we are uncertain of the effect on adverse events and pregnancy outcomes (live birth, clinical pregnancy, miscarriage). Dopamine agonists plus co-intervention may decrease moderate or severe OHSS rates compared to co-intervention only, but we are uncertain whether dopamine agonists affect pregnancy outcomes. When compared to other active interventions, we are uncertain of the effects of dopamine agonists on moderate or severe OHSS and pregnancy outcomes.

PLAIN LANGUAGE SUMMARY

Can dopamine agonists prevent ovarian hyperstimulation syndrome in women undergoing fertility treatment with IVF or ICSI?

Why we did this Cochrane Review

We wanted to find out whether dopamine agonists are effective and safe for preventing ovarian hyperstimulation syndrome (OHSS) in women at high risk of OHSS (e.g. women with polycystic ovaries or a high number of eggs following ovarian stimulation) undergoing in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI). How effective are these medicines compared to other types of medicines or withholding ovarian stimulation for a few days (called coasting))?

Background

IVF (eggs and sperm are mixed in a laboratory and the resulting embryo inserted into the womb) or ICSI (an IVF procedure where a single sperm cell is injected directly into an egg in a laboratory and the resulting embryo inserted into the womb) are treatments for infertility. To do these, the ovaries (female reproductive organs) are stimulated to produce more eggs by giving women a hormone medication. OHSS is a complication of the stimulation of the ovaries in IVF or ICSI treatment where too many eggs develop, the ovaries swell up, and fluid leaks into other parts of the body, resulting in bloating of the stomach, blood clots, and a reduction in blood and oxygen to important organs. In most cases, the condition is mild and resolves without treatment, but some women develop a moderate or severe form of OHSS that requires hospitalisation. There is no cure for OHSS other than waiting for it to settle down and managing the symptoms until they disappear.

Dopamine agonists are a medicine that could prevent the leaking of fluid from the blood vessels to other parts of the body, which is a major problem in OHSS.

Several treatments have been suggested to prevent OHSS. For example, coasting, or medications that keep fluid in the blood vessels (dopamine agonists, human albumin, hydroxyethyl starch, calcium, or diosmin) or support organ function (prednisolone).

What we found

We found 22 randomised controlled trials (a type of study that gives the most reliable evidence about the effects of a treatment) involving 3171 women at high risk of OHSS that evaluated three dopamine agonists (cabergoline, bromocriptine, and quinagolide). Six studies are new in this update. The main outcome measures were the number of new cases (incidence) of moderate or severe OHSS and live birth rate. The evidence is current to 4 May 2020**.**

Key results

Dopamine agonists versus placebo/no treatment

Dopamine agonists appear to reduce the incidence of moderate or severe OHSS in women at high risk of OHSS compared with placebo (a pretend treatment) or no treatment. This suggests that of every 100 women having IVF or ICSI, 27 women taking placebo or no treatment will have moderate or severe OHSS, compared to eight to 14 women taking dopamine agonists. Dopamine agonists may improve pregnancy outcomes, but we remain uncertain if it might increase mild side effects, such as stomach upsets, feeling sick, or dizziness. We are uncertain of the effect of dopamine agonists on pregnancy outcomes, as, pregnancy data were scarcely reported.

Dopamine agonist plus another treatment versus another treatment

Taking dopamine agonists combined with another active treatment may reduce the risk of moderate or severe OHSS compared to women taking another active treatment alone. This means that of 100 women having treatment with another active treatment alone for OHSS, 11 women will have moderate or severe OHSS compared to three to nine women using dopamine agonists plus another active treatment. We remain uncertain if dopamine combined with another treatment improves pregnancy outcomes and side effects.

Dopamine agonist versus another treatment

We are uncertain whether the dopamine agonist cabergoline decreases OHSS rates compared to other active treatments (e.g. hydroxyethyl starch, prednisolone, calcium infusion or coasting). We are uncertain whether cabergoline improves pregnancy outcomes compared with other interventions. There were no side effects in the only study for this comparison.

Quality of evidence

The quality of the evidence ranged from very low to moderate. Limitations included poor reporting of study methods and imprecision (too few events, too few included studies) for some comparisons.

SUMMARY OF FINDINGS

Summary of findings 1. Dopamine agonist versus placebo/no intervention

Dopamine agonist vs placebo/no intervention

Patient or population: women of reproductive age undergoing any ART therapy

Settings: ART unit

Intervention: dopamine agonist

Comparison: placebo/no intervention

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo/no intervention	Risk with dopamine agonist				
Incidence of moderate or severe OHSS	268 per 1000	105 per 1000 (78 to 139)	**OR 0.32** (0.23 to 0.44)	1202 (10 RCTs)	⊕⊕⊕⊖ **Moderate** [a]	—
Live birth rate	324 per 1000	315 per 1000 (223 to 426)	**OR 0.96** (0.60 to 1.55)	362 (3 RCTs)	⊕⊕⊖⊖ **Low** [a,b]	—
Clinical pregnancy rate	307 per 1000	289 per 1000 (218 to 377)	**OR 0.92** (0.63 to 1.37)	530 (5 RCTs)	⊕⊕⊖⊖ **Low** [a,b]	—
Multiple pregnancy rate	50 per 1000	17 per 1000 (1 to 303)	**OR 0.32** (0.01 to 8.26)	40 (1 RCT)	⊕⊖⊖⊖ **Very low** [a,b,c]	—
Miscarriage rate	72 per 1000	49 per 1000 (15 to 151)	**OR 0.66** (0.19 to 2.28)	168 (2 RCTs)	⊕⊕⊖⊖ **Low** [a,b]	—
Any other adverse events	43 per 1000	168 per 1000 (62 to 381)	**OR 4.54** (1.49 to 13.84)	264 (2 RCTs)	⊕⊖⊖⊖ **Very low** [a,b,d]	—

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

ART: assisted reproductive technology; **CI:** confidence interval; **OHSS:** ovarian hyperstimulation syndrome; **OR:** odds ratio; **RCT:** randomised controlled trial.

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded one level for risk of bias associated with poor reporting of study methods.
[b]Downgraded one level for serious imprecision; total number of events fewer than 400.
[c]Downgraded one level for serious indirectness; single small study.
[d]Downgraded one level for imprecision; wide confidence intervals.

Summary of findings 2. Dopamine agonist plus co-intervention versus co-intervention

Dopamine agonist plus co-intervention vs co-intervention

Patient or population: women of reproductive age undergoing any ART therapy

Settings: ART unit

Intervention: dopamine agonist plus co-intervention

Comparison: co-intervention

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with co-intervention only	Risk with dopamine agonist plus co-intervention				
Incidence of moderate or severe OHSS	109 per 1000	55 per 1000 (33 to 93)	**OR 0.48** (0.28 to 0.84)	748 (4 RCTs)	⊕⊕⊖⊖ **Low** [a,b]	—
Live birth rate	380 per 1000	426 per 1000 (332 to 525)	**OR 1.21** (0.81 to 1.80)	400 (2 studies)	⊕⊕⊖⊖ **Low** [a,b]	—
Clinical pregnancy rate	443 per 1000	469 per 1000 (398 to 542)	**OR 1.11** (0.83 to 1.49)	748 (4 studies)	⊕⊕⊖⊖ **Low** [a,b]	—
Multiple pregnancy rate	12 per 1000	24 per 1000	**OR 2.02**	166	⊕⊖⊖⊖ **Very low** [a,b,c]	—

		(2 to 217)	(0.18 to 22.77)	(1 study)		
Miscarriage rate	61 per 1000	41 per 1000 (19 to 85)	**OR 0.65** (0.30 to 1.42)	548 (3 studies)	⊕⊕⊖⊖ **Low** [a,b]	—
Any other adverse events	0 per 1000	0 per 1000 (0 to 0)	**OR 3.03** (0.12 to 75.28)	366 (2 studies)	⊕⊖⊖⊖ **Very low** [a,b,d]	—

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

ART: assisted reproductive technology; **CI:** confidence interval; **OHSS:** ovarian hyperstimulation syndrome; **OR:** odds ratio; **RCT:** randomised controlled trial.

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded one level for serious risk of bias associated with poor reporting of study methods.
[b]Downgraded one level for serious imprecision; total number of events fewer than 400.
[c]Downgraded one level for serious indirectness; single small study.
[d]Downgraded two levels for serious imprecision: wide confidence intervals.

Summary of findings 3. Dopamine agonist versus other active intervention

Dopamine agonist vs other active intervention

Patient or population: women of reproductive age undergoing any ART therapy

Settings: ART unit

Intervention: dopamine agonist

Comparison: other active intervention

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with other active intervention	Risk with dopamine agonist				

Incidence of moderate or severe OHSS	Cabergoline vs human albumin	432 per 1000	138 per 1000 (84 to 225)	**OR 0.21** (0.12 to 0.38)	296 (3 RCTs)	⊕⊖⊖⊖ **Very low** [a],b,c	—
	Cabergoline vs prednisolone	93 per 1000	27 per 1000 (5 to 120)	**OR 0.27** (0.05 to 1.33)	150 (1 RCT)	⊕⊖⊖⊖ **Very low** [a],b,d	—
	Cabergoline vs hydroxyethyl starch	67 per 1000	161 per 1000 (33 to 519)	**OR 2.69** (0.48 to 15.10)	61 (1 RCT)	⊕⊖⊖⊖ **Very low** [a],b,d	—
	Cabergoline vs coasting	125 per 1000	57 per 1000 (25 to 119)	**OR 0.42** (0.18 to 0.95)	320 (3 RCTs)	⊕⊖⊖⊖ **Very low** [a],b,c	—
	Cabergoline vs calcium infusion	60 per 1000	105 per 1000 (53 to 196)	**OR 1.83** (0.88 to 3.81)	400 (2 RCTs)	⊕⊖⊖⊖ Very l**ow** [a],b,c	—
	Cabergoline vs diosmin	120 per 1000	280 per 1000 (155 to 450)	**OR 2.85** (1.35 to 6.00)	200 (1 RCT)	⊕⊖⊖⊖ **Very low** [a],b,d	—
Live birth rate	Cabergoline vs coasting or calcium infusion	395 per 1000	414 per 1000 (323 to 510)	**OR 1.08** (0.73 to 1.59)	430 (2 RCTs)	⊕⊕⊖⊖ **Low** [a],b	—
Clinical pregnancy rate	Cabergoline vs human albumin, coasting, calcium infusion, or diosmin	432 per 1000	442 per 1000 (381 to 503)	**OR 1.04** (0.81 to 1.33)	1060 (7 RCTs)	⊕⊕⊕⊖ **Moderate** [a]	—
Multiple pregnancy rate	Cabergoline vs human albumin, coasting, or diosmin	130 per 1000	115 per 1000 (66 to 192)	**OR 0.87** (0.47 to 1.59)	400 (3 RCTs)	⊕⊕⊖⊖ **Low** [a],b	—
Miscarriage rate	Cabergoline vs human albumin, coasting, calcium infusion, or diosmin	79 per 1000	54 per 1000 (29 to 97)	**OR 0.66** (0.35 to 1.25)	630 (4 RCTs)	⊕⊕⊖⊖ **Low** [a],b	—
Any other adverse events	Cabergoline vs calcium infusion	0 per 1000	0 per 1000 (0 to 0)	Not estimable	170 (1 RCT)	Not estimable	—

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

ART: assisted reproductive technology; **CI:** confidence interval; **OHSS:** ovarian hyperstimulation syndrome; **OR:** odds ratio; **RCT:** randomised controlled trial.

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded one level for risk of bias associated with poor reporting of study methods.
[b]Downgraded one level for serious imprecision; total number of events fewer than 400.
[c]Downgraded one level for serious inconsistency; I^2 greater than 50.
[d]Downgraded one level for serious indirectness; single small study.

BACKGROUND

Description of the condition

Ovarian hyperstimulation syndrome (OHSS) is a complication of assisted reproduction technology (ART) treatment. It can occur following exposure of the ovaries of susceptible women to human chorionic gonadotrophin (hCG) or luteinising hormone (LH) during controlled ovarian stimulation with follicle-stimulating hormone (FSH). Women at risk of OHSS are generally young and have polycystic ovary syndrome (PCOS) (Costello 2012). OHSS is characterised by enlarged ovaries and an acute fluid shift from the intravascular space to the third space (mainly to the abdominal or thoracic cavity), which may result in an accumulation of fluid in the peritoneal cavity and pleura, an elevation of haematocrit, and a decrease in organ perfusion (Aboulghar 2003; Soares 2008; Vloeberghs 2009). Its symptoms range from abdominal bloating and a feeling of fullness to shortness of breath (Vloeberghs 2009). OHSS was classified as mild, moderate or severe by Golan and colleagues (Golan 1989), modified from Rabau and colleagues (Rabau 1967) by incorporating ultrasonographic measurement of the stimulated ovaries. Despite measures adopted by physicians to prevent these sequelae, mild OHSS may affect up to 33% of in vitro fertilisation (IVF) cycles. Moderate or severe OHSS arises in 3% to 8% of IVF cycles (RCOG 2006). Young women with low body mass index and polycystic ovaries are at particular risk of OHSS and the only way to avoid the condition for women with fallopian tube compromise, or whose partner has impaired semen parameters, is to undergo in vitro oocyte maturation, which is an approach that is not available in most centres (Walls 2015).

The pathophysiology of OHSS is not yet completely elucidated. Increased vascular permeability causing the loss of fluid into the third space (abdominal and pleural cavity) is the central feature of clinically significant OHSS, which triggers events that result in the associated symptoms (such as abdominal pain and distension) (Ata 2009). Most cases of OHSS have been associated with the use of hCG to trigger oocyte maturation prior to oocyte retrieval, however, it is recognised that hCG has no direct effect on the vascular system (Gómez 2002). Vasoactive substances are released by the ovaries in response to hCG administration. It is almost certain that vascular endothelial growth factor (VEGF) is a key substance that induces vascular hyperpermeability, leading to a shift of fluids from the intravascular system to the third space (Busso 2009; Soares 2008). Higher production of VEGF from the many follicles during stimulation by ovarian steroids and hCG appears to be the specific key process leading to the development of OHSS in women at high risk of OHSS.

Description of the intervention

Severe OHSS is a potentially life-threatening condition that occurs in women undergoing ART cycles. Several measures have been introduced to prevent OHSS (Prakash 2009). These include cycle cancellation or 'coasting' (D'Angelo 2017; Delvigne 2002), use of intravenous fluids (Youssef 2010; Youssef 2016), cryopreservation of embryos rather than immediate fresh embryo transfer (D'Angelo 2007), and the use of progesterone as luteal phase support rather than hCG (van der Linden 2015). More recent treatments include 'minimal stimulation IVF' (using a combination of medications to gently stimulate the ovaries), in vitro maturation of oocytes (letting oocytes mature in vitro) (Walls 2012), the use of 'natural cycle' IVF (collecting and fertilising one egg released during the normal monthly cycle and without the use of fertility drugs) (Edwards 2007), the use of metformin in women with PCOS (Tso 2014), the use of gonadotropin-releasing hormone (GnRH) antagonist, as opposed to GnRH agonist for ovarian downregulation (a prerequisite to assist in the timing of oocyte retrieval), adjusting stimulation protocols (Al-Inany 2011), and the use of an agonist trigger prior to oocyte retrieval in an antagonist cycle (Casper 2015). Despite their availability, there is no consensus on what would be the most favourable strategy to prevent OHSS, and none of these strategies have led to the eradication of OHSS (Aboulghar 2009). Research suggests that the use of dopamine agonists may be a promising strategy for the prevention and treatment of OHSS (Busso 2009; Castelo-Branco 2009).

How the intervention might work

With a better understanding of the pathophysiology of OHSS and recognition of the important role of VEGF in the development of OHSS, a series of blockers, such as SU5416 (a potent and selective inhibitor of the vascular endothelial growth factor receptor (VEGFR)), were introduced to reverse the hCG action on vascular permeability by targeting VEGFR-2 expressed on human ovaries (Gómez 2002). However, these anti-angiogenic drugs could not be used clinically to prevent or treat OHSS due to their adverse effect profile (such as thromboembolism) (Glade-Bender 2003; Kuenen 2003), and the possibility of affecting embryo implantation (Pauli 2005; Rockwell 2002). Another approach is to consider the use of a dopamine agonist, which shows similar effects to anti-angiogenic drugs on vascular permeability and appears not to exert adverse effects (Castelo-Branco 2009; Soares 2012). Moreover, dopamine agonists have been used for many years in other fields of medicine, for example to treat elevated serum prolactin levels. However, since the dopamine agonist cabergoline has been associated with fibrotic valvular heart disease when used chronically, other types of dopamine agonists are now being examined for use in OHSS. Possible advantages are the different pharmacokinetic profiles (e.g. shorter half-life of the drugs (about 17 hours for quinagolide versus about 65 hours for cabergoline)) thereby reducing exposure of embryos to possible teratogenic effects (Busso 2010), and in case of bromocriptine, lower costs and longer experience in use during pregnancy (Beltrame 2013).

Research findings in animal models of OHSS, as well as in humans, have shown that cabergoline can prevent the increase in vascular permeability (Gómez 2006). Several clinical trials have also evaluated the clinical value of cabergoline and showed that prophylactic use of cabergoline was associated with a decrease in the severity of OHSS (Manno 2005). Therefore, dopamine agonists may provide a new, specific, and non-toxic approach to the prevention and treatment of OHSS (Alvarez 2007a; Knoepfelmacher 2006).

Why it is important to do this review

Though short-term use of dopamine agonists for preventing OHSS represents no significant risk for women, long-term data on its effectiveness and safety requires corroboration. An increased incidence of cardiac valve regurgitation is suggested when women took cabergoline or pergolide for treating Parkinson's disease or hyperprolactinaemia (Budayr 2020; Kars 2008; Martin 2009; Schade 2007; Trifiro 2012; Zanettini 2007). Clinical studies have increasingly suggested that cabergoline can be safely administered in ART for preventing OHSS without influencing pregnancy outcomes.

Moreover, the role of other dopamine agonists (e.g. quinagolide and bromocriptine) for preventing OHSS remain uncertain due to lack of robust evidence for their efficacy and safety. This review aimed to summarise the available evidence from randomised controlled trials (RCTs) to determine whether dopamine agonists can reduce the incidence of moderate or severe OHSS in women at high risk of OHSS undergoing ART and identify any safety concerns.

OBJECTIVES

To assess the effectiveness and safety of dopamine agonists in preventing OHSS in women at high risk of developing OHSS when undergoing ART treatment.

METHODS

Criteria for considering studies for this review

Types of studies

All published and unpublished RCTs investigating the effectiveness and safety of dopamine agonists compared with placebo/no intervention or another intervention. We handled conference abstracts in the same way as full publications. We excluded quasi-randomised trials and, in the case of cross-over trials, included only pre-crossover data.

Types of participants

Women of reproductive age at high risk of OHSS (as defined by the studies) and undergoing any ART therapy.

Types of interventions

Trials were eligible for inclusion when they evaluated any dose of dopamine agonist alone or as an add-on therapy versus placebo, no intervention, or other active treatments.

Types of outcome measures

Both primary and secondary outcome measures were defined for this review.

Primary outcomes

- Incidence of moderate or severe OHSS (as determined by study authors) per woman randomised.
- Live birth rate (as a result of an embryo transferred in a fresh cycle using fertilised oocytes from the same menstrual cycle) defined as a live infant born after 20 weeks' gestation per woman randomised.

Secondary outcomes

- Clinical pregnancy rate (as a result of an embryo transferred in a fresh cycle using fertilised oocytes from the same menstrual cycle) per woman randomised.
- Multiple pregnancy rate (as a result of an embryo transferred in a fresh cycle using fertilised oocytes from the same menstrual cycle) per woman randomised.
- Miscarriage rate (following an embryo transferred in a fresh cycle using fertilised oocytes from the same menstrual cycle) per woman randomised.
- Any other adverse events of the treatment per woman randomised.

Search methods for identification of studies

See: Cochrane Gynaecology and Fertility (CGF) (formerly Menstrual Disorders and Subfertility Group, MDSG) guidance for writing all sections of systematic reviews (CGF).

We searched for published and unpublished articles in any language, that described or might have described RCTs of dopamine agonists (and more specifically cabergoline, quinagolide, or bromocriptine) for preventing OHSS, in consultation with the Cochrane Gynaecology and Fertility Information Specialist.

Electronic searches

We searched:

- the Cochrane Gynaecology and Fertility Group's Specialised Register using key terms on a Procite platform (searched 4 May 2020; Appendix 1). This register also contains unpublished trial abstracts;
- the Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies Online (CRSO), Web platform (searched 4 May 2020; Appendix 2; CENTRAL included the ongoing trials from clinicaltrials.gov and the World Health Organization International Clinical Trials Registry Platform);
- MEDLINE, Ovid (searched from 1946 to 4 May 2020; Appendix 3);
- Embase, Ovid (searched from 1980 to 4 May 2020; Appendix 4);
- PsycINFO, Ovid (searched from 1806 to 4 May 2020; Appendix 5);
- CINAHL, EBSCO (searched from 1961 to 4 May 2020; Appendix 6).

We also searched the Epistemonikos database, which contains systematic reviews that can be useful for reference checking for trials (www.epistemonikos.org/en).

We combined the MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials, which appears in the *Cochrane Handbook for Systematic Reviews of Interventions* (Chapter 4; Higgins 2019).

We combined the Embase searches with trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN; *(https://www.sign.ac.uk/what-we-do/methodology/search-filters/).*

Searching other resources

We searched the citation lists of relevant publications and included studies, review articles, and abstracts of conferences, and asked manufacturers, experts, and specialists in the field for any trials that they were aware of.

We conducted handsearching in the appropriate journals of gynaecology and reproductive medicine; the conference proceedings (for abstracts) of the European Society for Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM), as well as related textbooks.

We searched for conference abstracts on the Web of Science (wokinfo.com/).

Data collection and analysis

Selection of studies

Two review authors (SM and HT) independently reviewed the titles and abstracts of the trials, in accordance with the search protocol. We reviewed full-text articles and considered them for inclusion. If the published study was judged to contain insufficient information, we contacted trial authors. Two review authors (SM and HT) independently critically appraised the trials against the inclusion criteria. We resolved any disagreements by consensus or referral to a third review author (RH).

Data extraction and management

Two review authors (SM and HT) independently extracted data using a piloted data extraction form (Appendix 7). We compared the two sets of extracted data and resolved discrepancies by discussion. The data extraction forms included methodological quality. We included this information in the review and presented it in the Characteristics of included studies and Characteristics of excluded studies tables following the guidance of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019).

Assessment of risk of bias in included studies

Two review authors (SM and HT) independently critically assessed risk of bias in all included studies, including the following domains: sequence generation; allocation concealment; blinding of participants, personnel, and outcome assessors; incomplete outcome data; selective outcome reporting, and other bias (described in Cochrane's tool for assessing risk of bias) (Higgins 2011). We judged each domain at low risk of bias, high risk of bias, or unclear risk of bias for either a lack of information or uncertainty regarding the potential for bias, with any disagreements resolved by consensus or by a discussion with a third review author (RH).

Measures of treatment effect

We anticipated that all data would be dichotomous. We used the numbers of events in the control and intervention groups of each study to calculate odds ratios (OR) with 95% confidence intervals (CI).

Unit of analysis issues

The primary analysis unit was per woman randomised.

Dealing with missing data

Our meta-analysis used an intention-to-treat (ITT) approach, meaning that we included all women randomised in the analysis, in the groups to which they were randomised. In case of missing data, we contacted the trial authors by e-mail. We assumed that events did not occur in the women for whom data were unobtainable.

Assessment of heterogeneity

We carried out a test for statistical heterogeneity for each meta-analysis and assessed heterogeneity using the I^2statistic. This quantifies inconsistency, describing the impact of heterogeneity on the meta-analysis and measuring the degree of inconsistency across studies. We considered an I^2statistic less than 25% as low-level heterogeneity, 25% to 50% as moderate-level heterogeneity, and higher than 50% as high-level heterogeneity (Higgins 2019).

Assessment of reporting biases

We planned to use a funnel plot to assess the potential for reporting bias where 10 or more trials per comparison reported data.

Data synthesis

We considered whether the clinical and methodological characteristics of the included studies were sufficiently similar for meta-analysis to provide a clinically meaningful summary. We pooled data where appropriate, using the Mantel-Haenszel method. We used a fixed-effect model as we did not anticipate finding large amounts of heterogeneity. We combined data to calculate pooled ORs and 95% CIs in the following.

- Dopamine agonist versus placebo/no intervention, subgrouped by type of dopamine agonist (cabergoline versus quinagolide versus bromocriptine) and severity of OHSS.
- Dopamine agonist plus co-intervention versus co-intervention, subgrouped by type of dopamine agonist (if available) and type of co-intervention.
- Dopamine agonist versus other active interventions, subgrouped by type of dopamine agonist (if available) and type of other active intervention.

We performed statistical analyses using Review Manager 5 (Review Manager 2014).

Subgroup analysis and investigation of heterogeneity

We considered the following subgroup analyses to assess any differences in effect within these subgroups:

- type of dopamine agonist;
- type of co-intervention;
- type of other active interventions;
- severity of OHSS (severe OHSS versus moderate OHSS).

Sensitivity analysis

We performed sensitivity analyses for the primary outcome of moderate or severe OHSS to test whether the review conclusion would be different. We conducted a sensitivity analysis by changing the underlying model to random effects to determine any difference resulting from the choice of the fixed-effect model. We also considered excluding studies with high risk of bias for any domain.

Summary of findings and assessment of the certainty of the evidence

We generated a 'Summary of findings' table using GRADEpro and Cochrane methods (GRADEpro GDT 2015; Higgins 2011). This table evaluated the overall quality of the body of evidence for the main review comparison (dopamine agonists versus placebo or no intervention) for the main review outcomes (i.e. incidence of moderate or severe OHSS, live birth rate, multiple pregnancy rate, clinical pregnancy rate, miscarriage rate, and any other adverse effect). We also developed 'Summary of findings' tables for the comparisons of dopamine agonist plus co-intervention versus co-intervention and dopamine agonist versus other active intervention. According to GRADE criteria, we assessed the following factors that might decrease the quality level of a body of evidence: study limitations (i.e. risk of bias), consistency of effect, imprecision, indirectness, and publication bias. We incorporated

judgements about evidence quality (high, moderate, low, and very low) into reporting of results for each outcome. Two review authors (HT and SM) independently conducted evidence grading, and resolved disagreements by consensus.

RESULTS

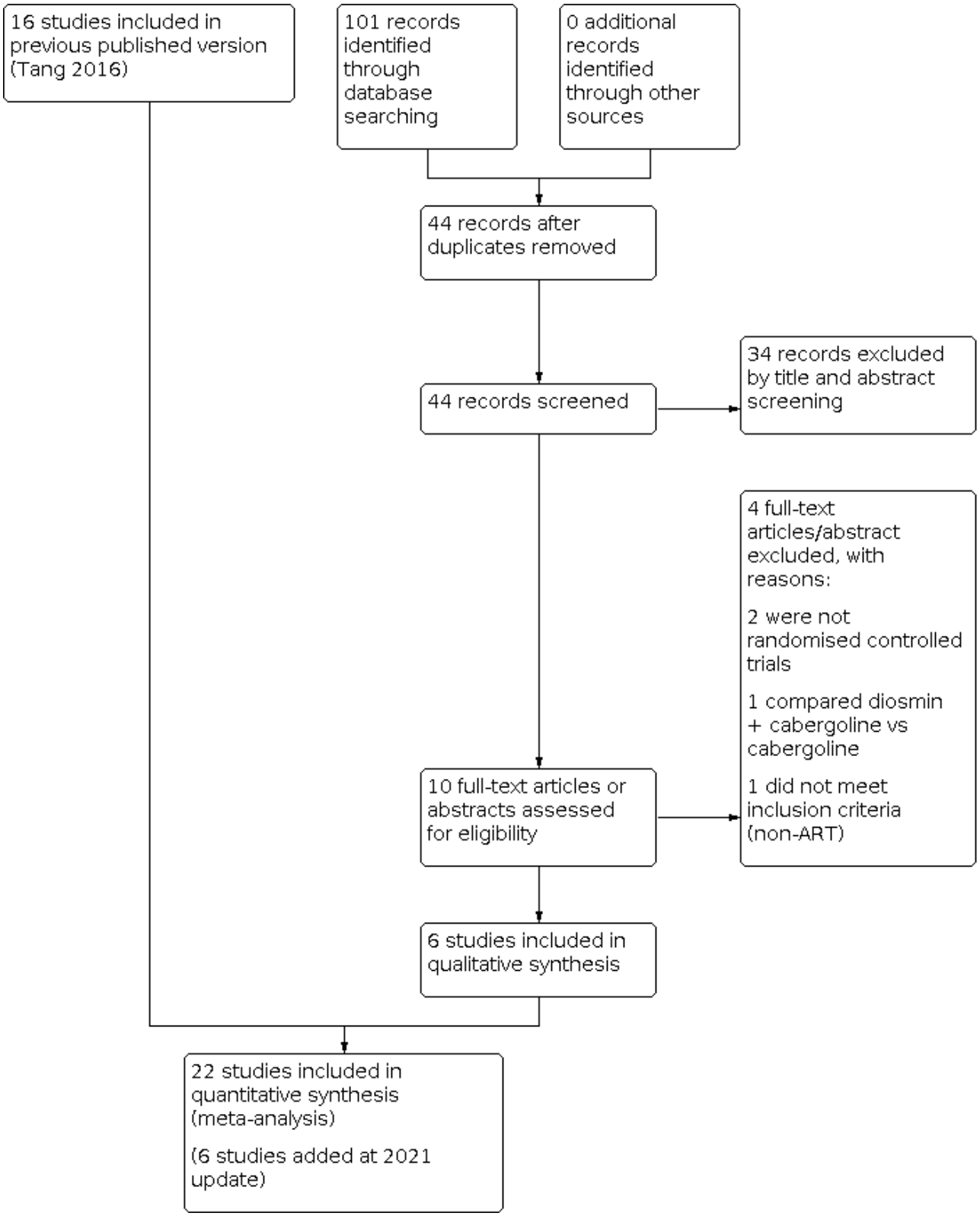
Description of studies

We included all RCTs in ART reporting on dopamine agonists for the prevention of OHSS.

Results of the search

This updated search was performed up to May 2020. In this 2021 updated review, we included six additional trials (Bassiouny 2018; Elnory 2018; El-Shaer 2019; Kilic 2015; Saad 2017; Singh 2017). This resulted in 22 included trials (Alhalabi 2011; Alvarez 2007a; Amir 2015; Bassiouny 2018; Beltrame 2013; Busso 2010; Carizza 2008; Dalal 2014; Elnory 2018; El-Shaer 2019; Fetisova 2014; Ghahiri 2015; Jellad 2017; Kilic 2015; Matorras 2013; Saad 2017; Salah 2012; Shaltout 2012; Singh 2017; Sohrabvand 2009; Tehraninejad 2012; Torabizadeh 2013). See Figure 1 for the PRISMA flow chart.

Figure 1. Study flow diagram search May 2020. ART: assisted reproduction technology.



We excluded 23 studies, of which three were excluded in the 2020 update (Saad 2019; Seyam 2018; Zahran 2018).

There are currently five ongoing studies, which will be checked in the future update (El Khattan 2015; Hendricks 2015; IRCT2016071428930N1; Kamel 2015; Khaled 2014). One meeting abstract is awaiting classification (Ahmadi 2010).

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; and Characteristics of ongoing studies tables.

Included studies

We included 22 studies (Alhalabi 2011; Alvarez 2007a; Amir 2015; Bassiouny 2018; Beltrame 2013; Busso 2010; Carizza 2008; Dalal 2014; Elnory 2018; El-Shaer 2019; Fetisova 2014; Ghahiri 2015; Jellad 2017; Kilic 2015; Matorras 2013; Saad 2017; Salah 2012; Shaltout 2012; Singh 2017; Sohrabvand 2009; Tehraninejad 2012; Torabizadeh 2013) (see Characteristics of included studies table). We contacted some trial authors for more detailed information (Dalal 2014; Fetisova 2014; Ghahiri 2015; Jellad 2017; Salah 2012; Shaltout 2012; Sohrabvand 2009; Tehraninejad 2012).

Participants

Twenty-two studies enrolled 3171 women at high risk of OHSS undergoing IVF or ICSI. One of these studies included only oocyte donors (Alvarez 2007a).

The studies were performed in 11 different countries: five studies in Egypt (Bassiouny 2018; Elnory 2018; El-Shaer 2019; Saad 2017; Shaltout 2012); four studies in Iran (Ghahiri 2015; Sohrabvand 2009; Tehraninejad 2012; Torabizadeh 2013); three in Spain (Alvarez 2007a; Busso 2010; Matorras 2013); two in Brazil (Beltrame 2013; Carizza 2008); two in India (Dalal 2014; Singh 2017); and one each from Syria (Alhalabi 2011), Israel (Amir 2015), United Arab Emirates (Salah 2012), Russia (Fetisova 2014), Tunisia (Jellad 2017), and Turkey (Kilic 2015).

One study included women with PCOS only (Salah 2012), without additional risk factors for OHSS (such as a minimum oestradiol (E_2 or number of follicles/oocytes retrieved), whereas other studies either excluded women with PCOS (Beltrame 2013), or included women with and without PCOS (Alhalabi 2011; Alvarez 2007a; Amir 2015; Bassiouny 2018; Busso 2010; Carizza 2008; Elnory 2018; Fetisova 2014; Ghahiri 2015; Jellad 2017; Kilic 2015; Matorras 2013; Saad 2017; Shaltout 2012; Singh 2017; Sohrabvand 2009; Tehraninejad 2012; Torabizadeh 2013).

The definition of 'high risk of OHSS' varied widely between studies; some used a minimum number of follicles of a certain diameter (18 or more over 12 mm at day of hCG (El-Shaer 2019; Jellad 2017); 20 or more over 12 mm at day of hCG (Alhalabi 2011; Amir 2015; Kilic 2015; Matorras 2013; Shaltout 2012), with or without a minimum E_2 level at day of hCG (greater than 2500 pg/mL (Dalal 2014 (mentioned only number of 20 or more follicles without mentioning size of follicles); Torabizadeh 2013); greater than 3000 pg/mL (Elnory 2018; Ghahiri 2015; Jellad 2017; Kilic 2015; Matorras 2013; Saad 2017; Sohrabvand 2009); greater than 3500 pg/mL (Bassiouny 2018; Shaltout 2012); greater than 4000 pg/mL (Alhalabi 2011; Amir 2015; Carizza 2008)). Five studies also incorporated the retrieval of 20 or more oocytes as a criterion (Alvarez 2007a; Ghahiri 2015; Sohrabvand 2009; Tehraninejad 2012; Torabizadeh 2013), whereas one study used transvaginal aspiration of 15 or more follicles (Fetisova 2014). Three studies also considered women with previous history of OHSS as high risk (Elnory 2018; Ghahiri 2015; Saad 2017). Two studies also included women with polycystic ovaries (i.e. more than 24 antral follicles at baseline ultrasound examination) (Elnory 2018; Saad 2017). One study included women with 13 or more follicles greater than 11 mm (Singh 2017). One study included only oocyte donors who consequently did not proceed to have an embryo transferred (Alvarez 2007a). Most studies selected women aged between 18 and 40 years.

Some studies excluded women with very high E_2 levels (greater than 5000 pg/mL (Kilic 2015; Matorras 2013; Shaltout 2012); greater than 6000 pg/mL (Busso 2010; Singh 2017)), because of their very high risk of developing OHSS, and assigned those women to cycle cancellation. One study excluded coasting cases, without stating when a woman was eligible for coasting (Jellad 2017). One study cancelled cycles after randomisation and cryopreserved all embryos when early OHSS was detected on embryo transfer day (Bassiouny 2018).

Interventions

Comparisons with cabergoline

Seven studies involving 701 women compared cabergoline with placebo or no intervention (Alvarez 2007a; Amir 2015; Fetisova 2014; Jellad 2017; Kilic 2015; Salah 2012; Singh 2017). Amir 2015 also used coasting in almost half of the women in both the intervention and control group. We tried to contact the authors to retrieve more information about which women received coasting and whether these women developed OHSS, but received no reply. Other studies excluded women who were received coasting.

Four studies gave oral cabergoline 0.5 mg daily for eight days from the day of hCG injection (Alvarez 2007a; Amir 2015; Jellad 2017; Kilic 2015), one study gave oral cabergoline 0.5 mg daily from the day after oocyte retrieval for five days before embryo transfer day (Fetisova 2014), and one study gave oral cabergoline 0.5 mg on two successive days, starting from the day of hCG injection and repeated one week later (Salah 2012). Salah 2012 also had a third treatment arm of oral prednisolone 10 mg daily from the day of hCG injection to the day of the pregnancy test (Salah 2012).

Two studies involving 382 women compared cabergoline plus hydroxyethyl starch (HES) versus HES alone (500 mL of HES by intravenous infusion during follicle aspiration plus oral cabergoline 0.5 mg daily for eight days starting on the day of hCG administration for Matorras 2013; 500 mL of HES by intravenous infusion on day of follicle aspiration and oral cabergoline 0.25 mg daily for eight days starting on the day of hCG administration for Shaltout 2012).

Two studies involving 235 women compared oral cabergoline 0.5 mg daily with human albumin (albumin 20 g 20% on day of oocyte retrieval and cabergoline for seven days beginning on the day of oocyte retrieval in Tehraninejad 2012; albumin 10 units 20% on day of oocyte retrieval and cabergoline for eight days beginning on the day of hCG injection in Torabizadeh 2013).

One study with 91 women involved three arms (oral cabergoline 0.5 mg daily for seven days after oocyte retrieval versus albumin (100 mL intravenous 30 minutes after retrieval within four hours) versus 6% HES 1000 mL intravenous 30 minutes after oocyte retrieval within four hours) (Ghahiri 2015).

One study involving 166 women compared cabergoline 0.5 mg daily for three weeks beginning the day after oocyte retrieval plus albumin 20 g on day of oocyte retrieval versus albumin 20 g alone (Carizza 2008).

Two studies involving 120 women compared cabergoline 0.5 mg daily for seven or eight days after hCG administration versus coasting with gonadotropin administration withheld until serum E_2 level was below 3000 pg/mL or serum E_2 level started to decline before hCG administration) (Dalal 2014; Sohrabvand 2009). However, Dalal 2014 also gave 6% HES to 58 women and the remaining included woman received an ascites tap instead of HES.

One study involving 300 women compared cabergoline plus coasting (stopping receiving human menopausal gonadotrophin (hMG) for one day while continuing agonist injections and cabergoline 0.25 mg/day for eight days from hCG administration) versus cabergoline (0.25 mg/day for eight days from hCG administration) versus coasting (stopping receiving hMG for one day while continuing agonist injections) (Bassiouny 2018).

Two studies involving 400 women compared oral cabergoline 0.5 mg daily for seven days starting at day of ovum pick-up with calcium infusion (10 mL of calcium gluconate 10%, in 200 mL 0.9% saline solution given intravenously on the day of ovum pick-up and days one, two, and three after day of ovum pick-up over 30 minutes) (Elnory 2018; El-Shaer 2019).

One study involving 200 women compared oral cabergoline 0.5 mg daily for eight days starting at day of hCG injection with oral diosmin 1000 mg/eight hours for two weeks starting at day of hCG injection (Saad 2017).

Comparisons with quinagolide

Two studies involving 454 women compared quinagolide versus placebo (quinagolide 150 µg daily for 15 days beginning on the day of hCG administration for Alhalabi 2011; three subgroups with doses of quinagolide 50 µg daily, 100 µg daily, and 200 µg daily from the day of hCG administration until the day of serum hCG test (which was 17 days, standard deviation 2 days, after oocyte retrieval) for Busso 2010).

Comparisons with bromocriptine

One trial involving 47 women compared bromocriptine 2.5 mg daily versus folic acid 2.0 mg daily (as a placebo), both for 14 days, beginning the day of hCG administration (Beltrame 2013).

Outcomes

All 22 included studies reported the incidence of severe or moderate OHSS but only six studies reported live birth rate (Bassiouny 2018; Busso 2010; Elnory 2018; Kilic 2015; Shaltout 2012; Singh 2017). Fifteen studies reported clinical pregnancy rate (Alvarez 2007a; Amir 2015; Bassiouny 2018; Busso 2010; Carizza 2008; Dalal 2014; Elnory 2018; Fetisova 2014; Kilic 2015; Matorras 2013; Saad 2017; Shaltout 2012; Singh 2017; Sohrabvand 2009; Tehraninejad 2012). Torabizadeh 2013 only reported pregnancy rates of the women who developed moderate or severe OHSS (no significant difference between groups) and Alhalabi 2011 and El-Shaer 2019 only mentioned that pregnancy rates were 'equal' between groups, without providing data on this outcome. Nine studies reported miscarriage rate (Amir 2015; Busso 2010; Carizza 2008; Dalal 2014; Fetisova 2014; Matorras 2013; Saad 2017; Shaltout 2012; Tehraninejad 2012), five studies reported multiple pregnancy rate (Amir 2015; Carizza 2008; Dalal 2014; Saad 2017; Tehraninejad 2012), and five studies reported any other adverse events of the treatment (Alvarez 2007a; Busso 2010; Carizza 2008; El-Shaer 2019; Shaltout 2012).

Excluded studies

We excluded 23 studies after examining full-text reports and obtaining clarifications from original authors. The reasons for exclusion are explained in the Characteristics of excluded studies table.

Studies awaiting classification

We classified one meeting abstract as awaiting classification due to lack of information for assessment despite attempts to contact the authors (Ahmadi 2010).

Ongoing studies

From the trial registries, five ongoing or recently finished trials had potential to be included in this review but were not published yet as abstracts or full-text papers (El Khattan 2015; Hendricks 2015; IRCT2016071428930N1; Kamel 2015; Khaled 2014).

Risk of bias in included studies

We assessed the risk of bias for each study using the Cochrane 'Risk of bias' tool (Higgins 2011). The 'Risk of bias' graph and 'Risk of bias' summary were presented in Figure 2 and Figure 3. We contacted the original authors by e-mail to clarify any information on methodological quality and study characteristics that were unclear (see 'Risk of bias' table in the Characteristics of included studies table).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

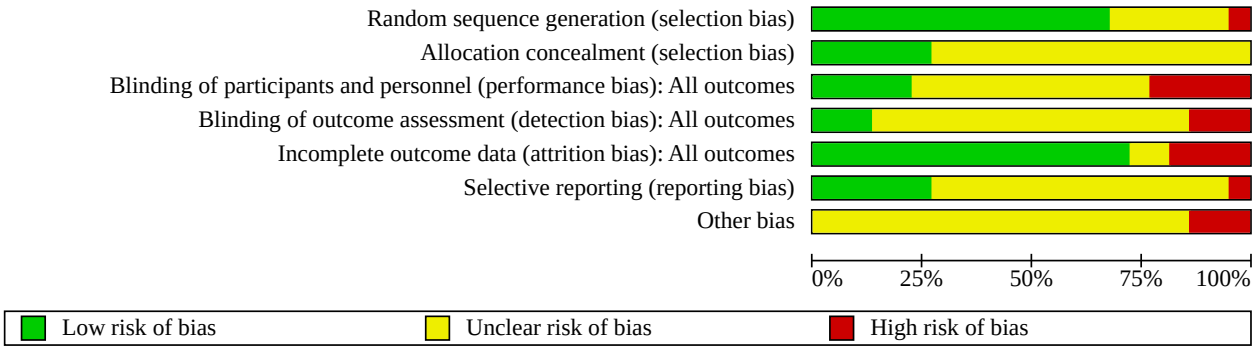


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

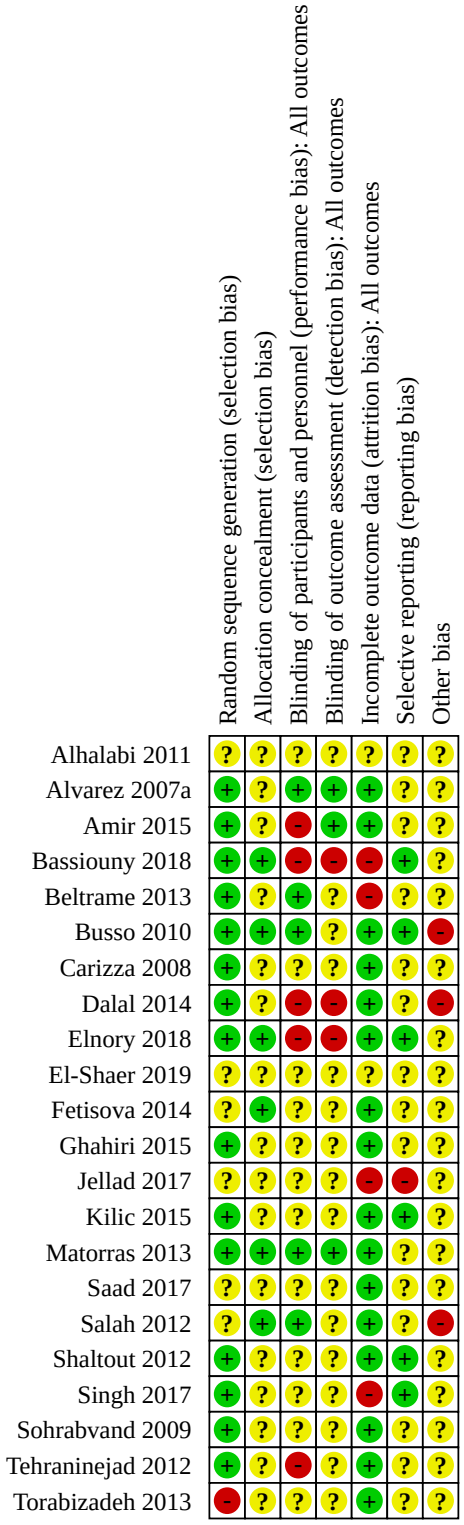


Figure 3. (Continued)

Allocation

Generation of random sequence

Fifteen trials clearly reported the generation of random sequence and were judged at low risk: fourteen trials used computer-generated randomisation (Alvarez 2007a; Amir 2015; Beltrame 2013; Busso 2010; Carizza 2008; Dalal 2014; Elnory 2018; Ghahiri 2015; Kilic 2015; Matorras 2013; Shaltout 2012; Singh 2017; Sohrabvand 2009; Tehraninejad 2012), and one trial reported using QuickCalcs to perform a block random to assign the participants into three groups (Bassiouny 2018). Six trials were assessed as unclear due to lack of information to judge the randomisation process (Alhalabi 2011; El-Shaer 2019; Fetisova 2014; Jellad 2017; Saad 2017; Salah 2012). One trial mentioned that randomised sampling was also performed by selecting "every other person," before actual randomisation took place, which we judged as high risk of bias (Torabizadeh 2013).

Allocation concealment

Six trials clearly reported the method of allocation concealment and were assessed at low risk of bias: five trials reported they allocated with sealed or closed envelopes (Bassiouny 2018; Busso 2010; Fetisova 2014; Matorras 2013; Salah 2012), and one study mentioned that the treatment allocation schedule was stored by an infertility consultant (Elnory 2018). The other 16 trials were judged unclear due to a lack of detailed allocation information (Alhalabi 2011; Alvarez 2007a; Amir 2015; Beltrame 2013; Carizza 2008; Dalal 2014; El-Shaer 2019; Ghahiri 2015; Jellad 2017; Kilic 2015; Saad 2017; Shaltout 2012; Singh 2017; Sohrabvand 2009; Tehraninejad 2012; Torabizadeh 2013).

Blinding

Performance bias

Performance bias was high in five studies due to lack of blinding of the participants or clinicians (Amir 2015; Bassiouny 2018; Dalal 2014; Elnory 2018; Tehraninejad 2012). Five studies were at low risk of performance bias (Alvarez 2007a; Beltrame 2013; Busso 2010; Matorras 2013; Salah 2012), and 12 studies were judged as unclear due to lack of information to perform judgement (Alhalabi 2011; Carizza 2008; El-Shaer 2019; Fetisova 2014; Ghahiri 2015; Jellad 2017; Kilic 2015; Saad 2017; Shaltout 2012; Singh 2017; Sohrabvand 2009; Torabizadeh 2013).

Detection bias

Three studies were at low risk of bias because they reported that the outcome assessor was blinded (Alvarez 2007a; Amir 2015; Matorras 2013); and three studies were at high risk of bias, as blinding was not performed (Bassiouny 2018; Dalal 2014; Elnory 2018). The other 16 studies were judged at unclear risk of bias, as information was inadequately reported for this domain (Alhalabi 2011; Beltrame 2013; Busso 2010; Carizza 2008; El-Shaer 2019; Fetisova 2014; Ghahiri 2015; Jellad 2017; Kilic 2015; Saad 2017; Salah 2012; Shaltout 2012; Singh 2017; Sohrabvand 2009; Tehraninejad 2012; Torabizadeh 2013).

Incomplete outcome data

Sixteen trials were at low risk of attrition bias (Alvarez 2007a; Amir 2015; Busso 2010; Carizza 2008; Dalal 2014; Elnory 2018; Fetisova 2014; Ghahiri 2015; Kilic 2015; Matorras 2013; Saad 2017; Salah 2012; Shaltout 2012; Sohrabvand 2009; Tehraninejad 2012; Torabizadeh 2013). Eleven studies reported the information on dropouts and described the exact reasons (Alvarez 2007a; Bassiouny 2018; Busso 2010; Dalal 2014; Elnory 2018; Ghahiri 2015; Kilic 2015; Saad 2017; Shaltout 2012; Singh 2017; Tehraninejad 2012). Two studies only stated that women withdrew from the study, without exact reasons (Carizza 2008; Salah 2012), but only a small proportion of women (less than 5%) were lost to follow-up, which does not have a clinically relevant impact on observed effect size, and hence we rated the studies at low risk of bias (Amir 2015; Fetisova 2014; Matorras 2013; Sohrabvand 2009; Torabizadeh 2013). Four trials were at high risk of bias (Bassiouny 2018; Beltrame 2013; Jellad 2017; Singh 2017): in two trials, women withdrew due to E_2 greater than 6000 pg/mL (Singh 2017) or OHSS (Bassiouny 2018), which affected the cases of OHSS reported. Beltrame 2013 had high dropout (40%) without mentioning reasons for dropout; Jellad 2017 only reported on the subgroups of women within each arm of the study that actually went on to develop OHSS while data from the non-OHSS participants were lacking. Two trials were at unclear due to lack of information to be judged (Alhalabi 2011; El-Shaer 2019).

Selective reporting

Six trials were at low risk of reporting bias because they reported the primary outcome of live birth rate (Bassiouny 2018; Busso 2010; Elnory 2018; Kilic 2015; Shaltout 2012; Singh 2017)).

One trial was judged as high risk of bias due to the fact that pregnancy and miscarriage rates were reported only for the women per arm that actually developed OHSS (Jellad 2017). The remaining 15 studies were at unclear risk of bias (Alhalabi 2011; Alvarez 2007a; Amir 2015; Beltrame 2013; Carizza 2008; Dalal 2014; El-Shaer 2019; Fetisova 2014; Ghahiri 2015; Matorras 2013; Saad 2017; Salah 2012; Sohrabvand 2009; Tehraninejad 2012; Torabizadeh 2013).

Other potential sources of bias

Three trials were at high risk of other bias (Busso 2010; Dalal 2014; Salah 2012): one trial included young women with PCOS without other high-risk factors identified (e.g. based on E_2 or ultrasound) (Salah 2012). Dalal 2014 reported that 29 participants in both groups also received HES infusion, and one participant from each group also had ascites drained but it was unclear who exactly received these extra interventions.

Effects of interventions

See: **Summary of findings 1** Dopamine agonist versus placebo/no intervention; **Summary of findings 2** Dopamine agonist plus co-intervention versus co-intervention; **Summary of findings 3** Dopamine agonist versus other active intervention

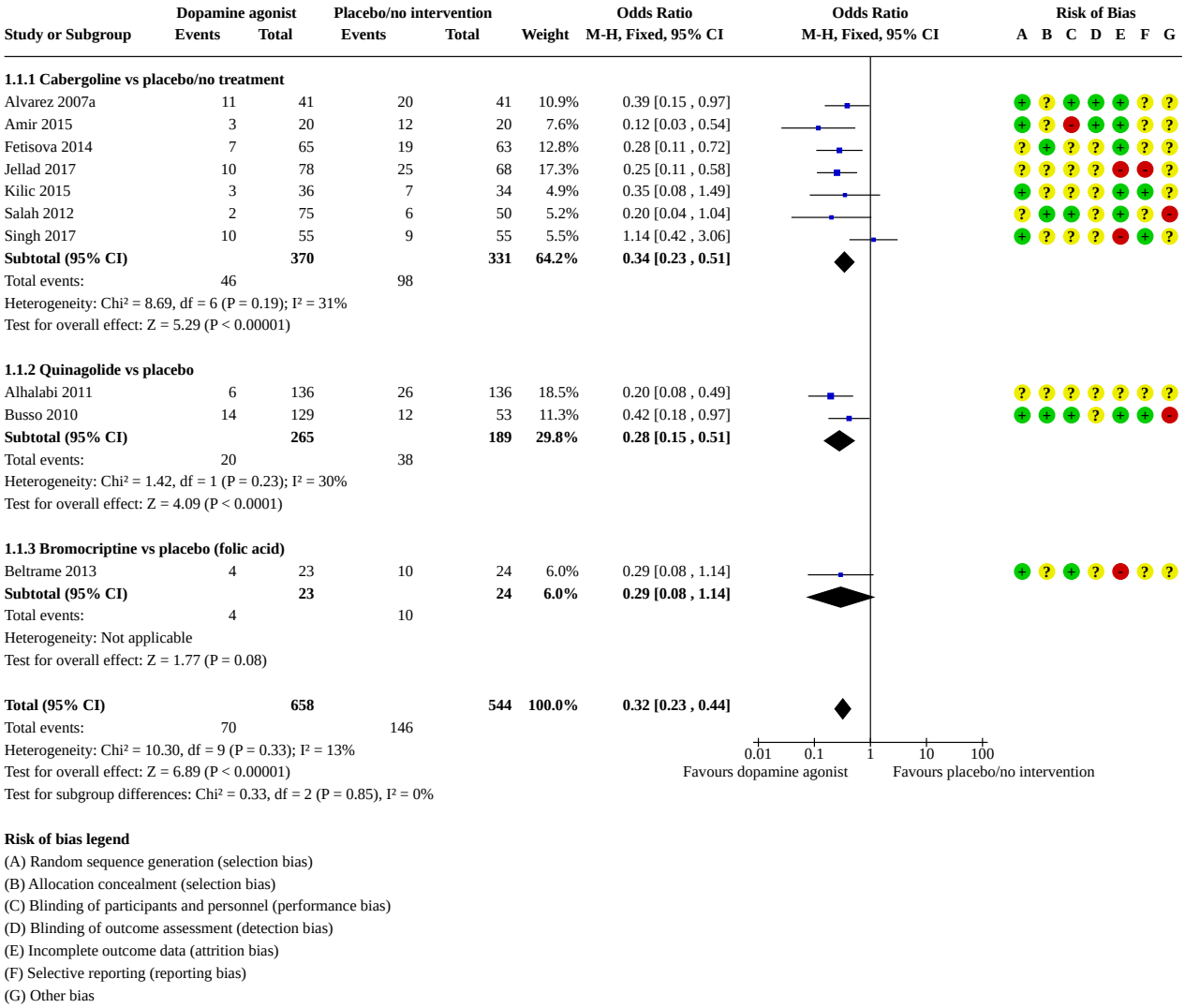
1. Dopamine agonist versus placebo/no intervention

1.1. Primary outcomes

1.1.1. Incidence of moderate or severe ovarian hyperstimulation syndrome

Ten studies reported the incidence of moderate or severe OHSS (Alhalabi 2011; Alvarez 2007a; Amir 2015; Beltrame 2013; Busso 2010; Fetisova 2014; Jellad 2017; Kilic 2015; Salah 2012; Singh 2017). Dopamine agonists were probably associated with a lower risk of moderate or severe OHSS than placebo/no intervention (OR 0.32, 95% CI 0.23 to 0.44; 10 studies, 1202 participants; I^2 = 13%; moderate-quality evidence; Analysis 1.1; Figure 4). This suggests that if the risk of moderate or severe OHSS following placebo/no intervention is assumed to be 27%, the risk following dopamine agonists would be between 8% and 14%.

Figure 4. Forest plot of comparison 1: Dopamine agonist (without co-intervention) versus placebo/no intervention, outcome: 1.1 moderate or severe ovarian hyperstimulation syndrome.



Subgroup analysis

We performed a subgroup analysis by type of dopamine agonist, which showed no evidence of a difference among these three types of dopamine agonist (P = 0.85). When compared with placebo/no intervention, cabergoline (OR 0.34, 95% CI 0.23 to 0.51; I^2 = 31%; 7 studies, 701 participants), and quinagolide (OR 0.28, 95% CI 0.15 to 0.51; I^2 = 30%; 2 studies, 454 participants) were associated with a lower risk of moderate or severe OHSS (Analysis 1.1; Figure 4). However, there was probably little or no difference between bromocriptine and placebo (OR 0.29, 95% CI 0.08 to 1.14; 1 study, 47 participants) (Analysis 1.1; Figure 4). Also, for the subgroup analysis by severity of OHSS, there was no difference between severe OHSS and moderate OHSS (P = 0.77). Dopamine agonists probably improve the risk of both severe OHSS (OR 0.27, 95% CI 0.14 to 0.51; I^2 = 0%; 9 studies, 930 participants) and moderate OHSS (OR 0.46, 95% CI 0.31 to 0.68; I^2 = 2%; 9 studies, 930 participants) when compared to placebo or no intervention (Analysis 1.2).

Sensitivity analysis

We conducted a prespecified sensitivity analysis by excluding four studies with high risk of bias from Analysis 1.1, the lower incidence of moderate or severe OHSS with dopamine agonists compared with placebo/no intervention remained unchanged (OR 0.28, 95% CI 0.17 to 0.46; I^2 = 0%; 10 studies, 552 participants). Also, use of a random-effects model did not affect the results.

1.1.2. Live birth rate

Three trials reported data on live birth rate (Busso 2010; Kilic 2015; Singh 2017). We are uncertain of the effect of dopamine agonists on live birth rate compared with placebo/no intervention (OR 0.96, 95% CI 0.60 to 1.55; I^2 = 0%; 3 studies, 362 participants; low-quality evidence; Analysis 1.3). This suggests that if the chance of live birth following placebo/no intervention is assumed to be 32%, the risk following dopamine agonists would be between 22% and 43%. In the subgroup analysis by type of dopamine agonist, the test for subgroup differences showed we are uncertain of an effect of cabergoline compared to placebo/no intervention (OR 0.91, 95% CI 0.44 to 1.87; I^2 = 0%; 2 studies, 180 participants) and the effect of quinagolide compared to placebo/no intervention (OR 1.01, 95% CI 0.53 to 1.91; 1 study, 182 participants), with a P value of 0.83.

1.2. Secondary outcomes

1.2.1. Clinical pregnancy rate

Five trials reported clinical pregnancy rate (Amir 2015; Busso 2010; Fetisova 2014; Kilic 2015; Singh 2017). We are uncertain of the effect of dopamine agonist when compared to placebo/no intervention (OR 0.92, 95% CI 0.63 to 1.37; I^2 = 0%; 5 studies, 530 participants; low-quality evidence; Analysis 1.4). This suggests that if the chance of clinical pregnancy following placebo/no intervention is assumed to be 31%, the risk following dopamine agonists would be between 22% and 38%. We are uncertain of the effect of between cabergoline compared to placebo/no intervention (OR 1.00, 95% CI 0.61 to 1.64; I^2 = 0%; 4 studies, 348 participants), and between quinagolide compared to placebo (OR 0.81, 95% CI 0.43 to 1.54; 1 study, 182 participants).

1.2.2. Multiple pregnancy rate

One study reported multiple pregnancy rate (Amir 2015). We are uncertain whether dopamine agonist improves multiple pregnancy rate compared with placebo/no intervention (OR 0.32, 95% CI 0.01 to 8.26; 1 study, 40 participants; very low-quality evidence; Analysis 1.5). This suggests that if the chance of multiple pregnancy following placebo/no intervention is assumed to be 5%, the risk following dopamine agonists would be between 1% and 30%.

1.2.3. Miscarriage rate

Two studies reported miscarriage rate (Amir 2015; Fetisova 2014). We are uncertain of the effect of dopamine agonist on miscarriage rate compared with placebo/no intervention (OR 0.66, 95% CI 0.19 to 2.28; I^2 = 0%; 2 studies, 168 participants; low-quality evidence; Analysis 1.6). This suggests that if the risk of miscarriage following placebo/no intervention is assumed to be 7%, the risk following dopamine agonists would be between 2% and 15%.

1.2.4. Any other adverse events of the treatment

Two trials reported adverse events (Alvarez 2007a; Busso 2010). We are uncertain whether dopamine agonists increased risk of adverse events (OR 4.54, 95% CI 1.49 to 13.84; I^2 = 49%; 2 studies, 264 participants; very low-quality evidence; Analysis 1.7). This suggests that if the risk of any other adverse events following placebo/no intervention is assumed to be 4%, the risk following dopamine agonists would be between 6% and 38%. Subgroup analysis by type of dopamine agonist showed no difference among dopamine agonists (P = 0.21).

We are uncertain whether cabergoline increases adverse effects compared to placebo/no intervention (OR 2.24, 95% CI 0.62 to 8.14; 1 study; 82 participants; Analysis 1.7). One trial reported that 17 women in the quinagolide group discontinued because of adverse events and no women in the placebo group (OR 16.64, 95% CI 0.98 to 282.02; 1 study; 182 participants) (Analysis 1.7).

2. Dopamine agonist plus co-intervention versus co-intervention

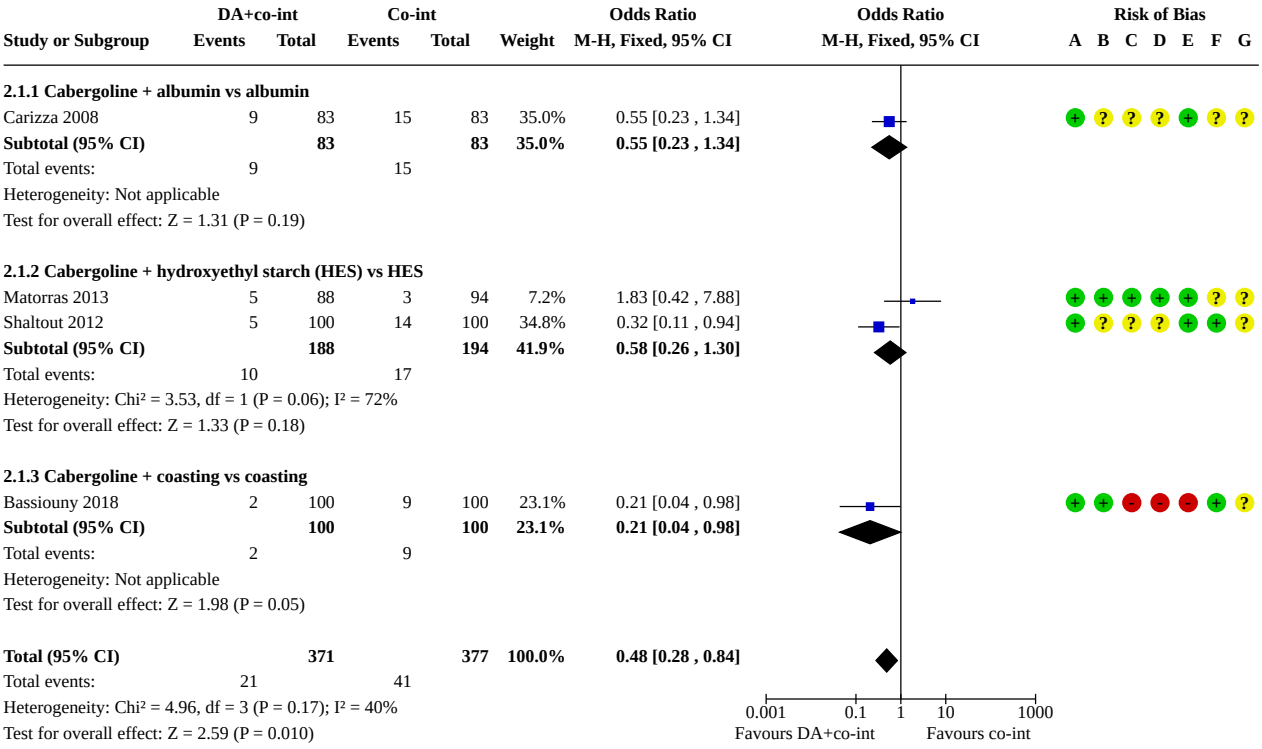
Four studies compared dopamine agonist plus co-intervention versus co-intervention (Bassiouny 2018; Carizza 2008; Matorras 2013; Shaltout 2012). All four studies used cabergoline. The co-interventions were HES (Matorras 2013; Shaltout 2012), albumin (Carizza 2008), and coasting (Bassiouny 2018).

2.1. Primary outcomes

2.1.1. Incidence of severe or moderate ovarian hyperstimulation syndrome

Four studies reported the incidence of moderate or severe OHSS (Bassiouny 2018; Carizza 2008; Matorras 2013; Shaltout 2012). Dopamine agonists plus co-intervention may decrease the risk of moderate or severe OHSS compared with co-intervention alone (OR 0.48, 95% CI 0.28 to 0.84; I^2 = 40%; 4 studies, 748 participants; low-quality evidence; Analysis 2.1; Figure 5). This suggests that if the risk of moderate or severe OHSS following placebo/no intervention is assumed to be 11%, the risk following dopamine agonists would be between 3% and 9%. Subgroup analysis by type of co-intervention did not alter this conclusion. We were uncertain of the effects between the following: cabergoline plus albumin group versus albumin group (OR 0.55, 95% CI 0.23 to 1.34; 1 study, 166 participants), cabergoline plus HES group versus HES group (OR 0.58, 95% CI 0.26 to 1.30; I^2 = 72%; 2 studies, 382 participants), or between cabergoline plus coasting group versus coasting group (OR 0.21, 95% CI 0.04 to 0.98; 1 study, 200 participants); all were low-quality evidence (Analysis 2.1; Figure 5).

Figure 5. Forest plot of comparison: 2 Dopamine agonist plus co-intervention versus co-intervention, outcome: 2.1 Moderate or severe ovarian hyperstimulation syndrome.



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Our sensitivity analysis by excluding one study (Bassiouny 2018) with high risk of bias (OR 0.57, 95% CI 0.31 to 1.03; I^2 = 44%; 3 studies, 548 participants) or changing analysis model (OR 0.50, 95% CI 0.23 to 1.08; I^2 = 40%; 4 studies, 748 participants) did not change these results.

2.1.2. Live birth rate

Two trials reported data on live birth rate (Bassiouny 2018; Shaltout 2012). We are uncertain of the effect of dopamine agonist plus co-intervention on live birth rate compared with co-intervention alone (OR 1.21, 95% CI 0.81 to 1.80; I^2 = 0%; 2 studies, 400 participants; low-quality evidence). This suggests that if the chance of live birth following placebo/no intervention is assumed to be 38%, the risk following dopamine agonists would be between 33% and 53%. Subgroup analysis by type of co-intervention showed no difference between subgroups (P = 0.49). We are uncertain whether cabergoline plus HES improved live birth compared to HES alone (OR 1.04, 95% CI 0.59 to 1.86; 1 study, 200 participants) or of cabergoline plus coasting compared to coasting alone (OR 1.38, 95% CI 0.79 to 2.42; 1 study, 200 participants) (Analysis 2.2).

2.2. Secondary outcomes

2.2.1. Clinical pregnancy rate

Four trials reported the clinical pregnancy rate (Bassiouny 2018; Carizza 2008; Matorras 2013; Shaltout 2012). We are uncertain of the effect of dopamine agonist plus co-intervention versus co-intervention alone (OR 1.11, 95% CI 0.83 to 1.49; I^2 = 0%; 4 studies, 748 participants; low-quality evidence; Analysis 2.3). This suggests that if the chance of clinical pregnancy following placebo/no intervention is assumed to be 44%, the risk following dopamine agonists would be between 40% and 54%. In the subgroup analysis, we found no difference between subgroups (P = 0.47). We are uncertain whether cabergoline plus albumin improved clinical pregnancy rate compared to albumin (OR 1.05, 95% CI 0.56 to 1.96; 1 study, 166 participants), cabergoline plus HES compared to HES (OR 0.98, 95% CI 0.65 to 1.47; I^2 = 0%; 2 studies, 382 participants), or cabergoline plus coasting compared to coasting (OR 1.49, 95% CI 0.86 to 2.61; 1 study, 200 participants; Analysis 2.3).

2.2.2. Multiple pregnancy rate

One study reported multiple pregnancy rate (Carizza 2008). We are uncertain of the effect of cabergoline plus albumin on multiple

pregnancy rate compared with albumin (OR 2.02, 95% CI 0.18 to 22.77; 1 study, 166 participants; very low-quality evidence; Analysis 2.4). This suggests that if the chance of multiple pregnancy following placebo/no intervention is assumed to be 1%, the risk following dopamine agonists would be between 0.2% and 22%.

2.2.3. Miscarriage rate

Three studies reported miscarriage rate (Carizza 2008; Matorras 2013; Shaltout 2012). We are uncertain of the effect of dopamine agonist plus co-intervention on miscarriage rates compared with co-intervention (OR 0.65, 95% CI 0.30 to 1.42; I^2 = 0%; 3 studies, 548 participants; low-quality evidence; Analysis 2.5). This suggests that if the risk of miscarriage following placebo/no intervention is assumed to be 6%, the risk following dopamine agonists would be between 2% and 9%. We found no difference between subgroups (P = 0.52) and the results showed that we are uncertain whether cabergoline plus albumin compared to albumin (OR 0.33, 95% CI 0.03 to 3.19; 1 study, 166 participants), or cabergoline plus HES compared to HES (OR 0.73, 95% CI 0.31 to 1.68; I^2 = 0%; 2 studies, 382 participants) improved miscarriage rate (Analysis 2.5).

2.2.4. Any other adverse events of the treatment

Two trials reported adverse events (Carizza 2008; Shaltout 2012). We are uncertain whether dopamine agonist plus co-intervention increases risk of adverse events (OR 3.03, 95% CI 0.12 to 75.28; I^2 = 0%; 2 studies, 366 participants; very low-quality evidence; Analysis 2.6. One trial with 166 participants detected no adverse events (Carizza 2008).

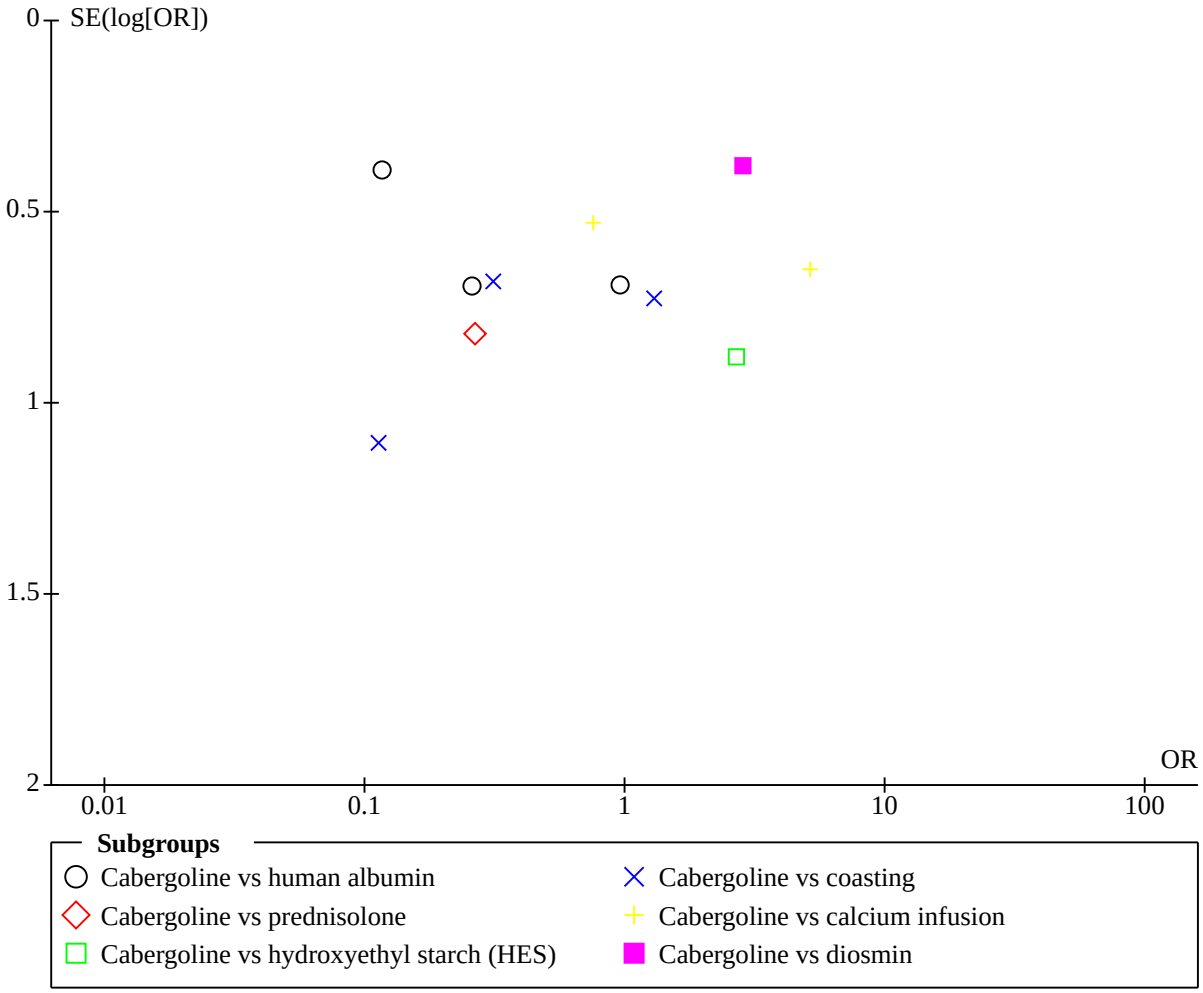
3. Dopamine agonist versus other active intervention

3.1. Primary outcomes

3.1.1. Incidence of moderate or severe ovarian hyperstimulation syndrome

Ten studies reported the incidence of moderate or severe OHSS when comparing dopamine agonist with several other active interventions (Bassiouny 2018; Dalal 2014; Elnory 2018; El-Shaer 2019; Ghahiri 2015; Saad 2017; Salah 2012; Sohrabvand 2009; Tehraninejad 2012; Torabizadeh 2013). There was significant heterogeneity between subgroups, therefore, we reported the results of each subgroup only (Figure 6).

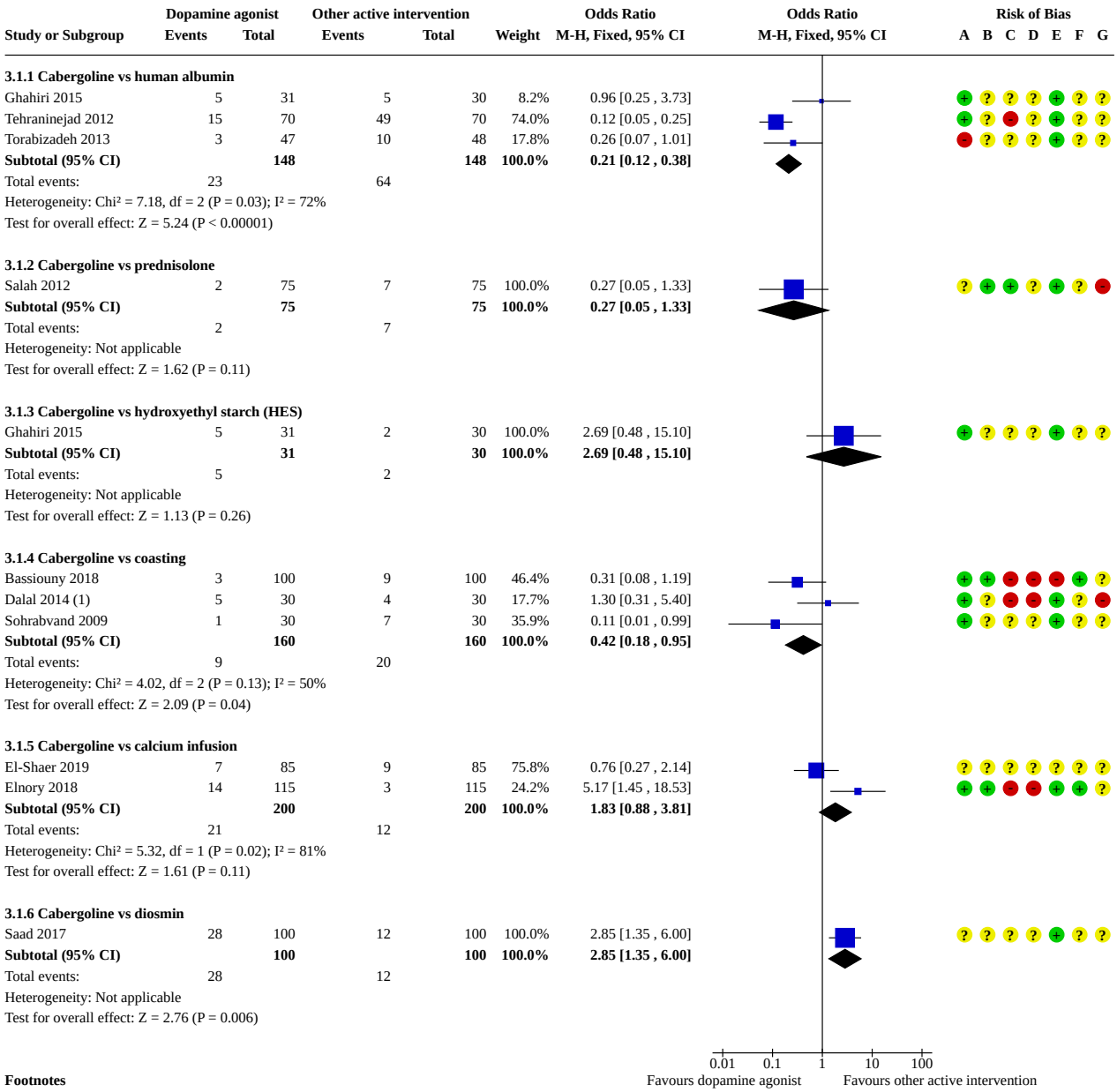
Figure 6. Funnel plot of comparison: 3 Dopamine agonist versus other active interventions, outcome: 3.1 Incidence of moderate or severe ovarian hyperstimulation syndrome (OHSS).



3.1.1.1. Cabergoline versus human albumin

Three studies reported the incidence of moderate or severe OHSS (Ghahiri 2015; Tehraninejad 2012; Torabizadeh 2013). We are uncertain whether cabergoline decreases the incidence of severe or moderate OHSS compared with human albumin (OR 0.21, 95% CI 0.12 to 0.38; I^2 = 72%; 3 studies, 296 participants; very low-quality evidence; Analysis 3.1; Figure 7). This suggests that if the risk of moderate or severe OHSS following human albumin is assumed to be 43%, the risk following dopamine agonists would be between 8% and 23%.

Figure 7. Forest plot of comparison 3: Cabergoline versus active interventions, outcome: 3.1 moderate or severe ovarian hyperstimulation syndrome.



Footnotes

(1) Both groups also received a background treatment of HES.

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

3.1.1.2. Cabergoline versus prednisolone

One study reported the incidence of moderate or severe OHSS (Salah 2012). We are uncertain of the effect of cabergoline on risk of moderate or severe OHSS compared with prednisolone (OR 0.27, 95% CI 0.05 to 1.33; 1 study, 150 participants; very low-quality evidence; Analysis 3.1; Figure 7). This suggests that if the risk of moderate or severe OHSS following prednisolone is assumed to be 9%, the risk following dopamine agonists would be between 0.5% and 12%.

3.1.1.3. Cabergoline versus hydroxyethyl starch

One study reported the incidence of moderate or severe OHSS (Ghahiri 2015). We are uncertain of the effect of cabergoline on risk of moderate or severe OHSS compared with HES (OR 2.69, 95% CI 0.48 to 15.10; 1 study, 61 participants; very low-quality evidence; Analysis 3.1; Figure 7). This suggests that if the risk of moderate or severe OHSS following HES is assumed to be 7%, the risk following dopamine agonists would be between 3% and 52%.

3.1.1.4. Cabergoline versus coasting

Three studies reported the incidence of moderate or severe OHSS (Bassiouny 2018; Dalal 2014; Sohrabvand 2009). We are uncertain whether cabergoline decreases the risk of moderate or severe OHSS compared with coasting (OR 0.42, 95% CI 0.18 to 0.95; I^2 = 50%; 3 studies, 320 participants; very low-quality evidence; Analysis 3.1; Figure 7). This suggests that if the risk of moderate or severe OHSS following coasting is assumed to be 13%, the risk following dopamine agonists would be between 3% and 12%.

3.1.1.5. Cabergoline versus calcium infusion

Two studies reported the incidence of moderate or severe OHSS (Elnory 2018; El-Shaer 2019). We are uncertain of the effect of cabergoline on risk of moderate or severe OHSS when compared with calcium infusion (OR 1.83, 95% CI 0.88 to 3.81; I^2 = 81%; 2 studies, 400 participants; very low-quality evidence; Analysis 3.1; Figure 7). This suggests that if the risk of moderate or severe OHSS following calcium infusion is assumed to be 6%, the risk following dopamine agonists would be between 5% and 20%.

3.1.1.6. Cabergoline versus diosmin

One study reported the incidence of moderate or severe OHSS (Saad 2017). We are uncertain of the effect of cabergoline on risk of moderate or severe OHSS compared with diosmin (OR 2.85, 95% CI 1.35 to 6.00; 1 study, 200 participants; very low-quality evidence; Analysis 3.1; Figure 7). This suggests that if the risk of moderate or severe OHSS following diosmin is assumed to be 12%, the risk following dopamine agonists would be between 16% and 45%.

3.1.2. Live birth rate

Two studies reported the data on live birth rate (Bassiouny 2018; Elnory 2018). We are uncertain whether dopamine agonist improves live birth rate (OR 1.08, 95% CI 0.73 to 1.59; I^2 = 0%; 2 studies, 430 participants; low-quality evidence) (Analysis 3.2). This suggests that if the chance of live birth following other active intervention is assumed to be 40%, the risk following dopamine agonist would be between 32% and 51%. Both trials included cabergoline. Our subgroup analysis by type of other active intervention showed that we are uncertain whether cabergoline improves live birth rate when compared to coasting (OR 1.04, 95% CI 0.59 to 1.83; 1 study, 200 participants) and when compared to calcium infusion (OR 1.11, 95% CI 0.66 to 1.89; 1 study, 230 participants) (Analysis 3.2).

3.2. Secondary outcomes

3.2.1. Clinical pregnancy rate

Seven studies reported clinical pregnancy rate (Bassiouny 2018; Dalal 2014; Elnory 2018; El-Shaer 2019; Saad 2017; Sohrabvand 2009; Tehraninejad 2012). The pooled results showed probably little or no difference in clinical pregnancy rate between dopamine agonists compared with other active interventions (OR 1.04, 95% CI 0.81 to 1.33; I^2 = 11%; 7 studies, 1060 participants; moderate-quality evidence). This suggests that if the chance of clinical pregnancy following other active intervention is assumed to be 43%, the risk following dopamine agonist would be between 38% and 50%. All trials evaluated the dopamine agonist cabergoline. Subgroup analysis by type of other active intervention showed that we were uncertain whether cabergoline improves clinical pregnancy rates when compared to human albumin (OR 0.68, 95% CI 0.33 to 1.38; 1 study, 140 participants), coasting (OR 1.46, 95% CI 0.92 to 2.32; I^2 = 28%; 3 studies, 320 participants), calcium infusion (OR 1.00, 95% CI 0.67 to 1.49; I^2 = 0%; 2 studies, 400 participants), or diosmin (OR 0.89, 95% CI 0.51 to 1.55; I^2 = 0%; 1 study, 200 participants) (Analysis 3.3).

3.2.2. Multiple pregnancy rate

Three studies reported multiple pregnancy rate (Dalal 2014; Saad 2017; Tehraninejad 2012). We are uncertain of the effect of dopamine agonist on multiple pregnancy rate (OR 0.87, 95% CI 0.47 to 1.59; I^2 = 0%; 3 studies, 400 participants; low-quality evidence; Analysis 3.4). Subgroup analysis by type of other active intervention showed that we were uncertain of the effect of cabergoline on multiple pregnancy rate when compared to human albumin (OR 0.58, 95% CI 0.13 to 2.54; 1 study, 140 participants), coasting (OR 5.35, 95% CI 0.25 to 116.31; 1 study, 60 participants), or diosmin (OR 0.83, 95% CI 0.41 to 1.67; 1 study, 200 participants) (Analysis 3.4).

3.2.3. Miscarriage rate

Four studies reported the miscarriage rate (Dalal 2014; Elnory 2018; Saad 2017; Tehraninejad 2012). We are uncertain of the effect of dopamine agonist on miscarriage rate (OR 0.66, 95% CI 0.35 to 1.25; I^2 = 0%; 4 studies, 630 participants; low-quality evidence; Analysis 3.5). Furthermore, in our subgroup analysis by type of other active intervention, we were uncertain of the effect of cabergoline on miscarriage rate when compared to human albumin (OR 0.32, 95% CI 0.03 to 3.19; 1 study, 140 participants), coasting (OR 0.19, 95% CI 0.01 to 4.06; 1 study, 60 participants), calcium infusion (OR 0.63, 95% CI 0.27 to 1.48; 1 study, 230 participants), or diosmin (OR 1.21, 95% CI 0.36 to 4.11; 1 study, 200 participants) (Analysis 3.5).

3.2.4. Any other adverse effects of the treatment

One study reported that there were no adverse events when comparing cabergoline versus calcium infusion (Analysis 3.6) (El-Shaer 2019).

DISCUSSION

Summary of main results

This systematic review evaluated the effectiveness and safety of dopamine agonists for preventing OHSS in women at high risk of OHSS during ART treatment and performed meta-analyses. Ten trials compared dopamine agonist with placebo or no intervention, four trials compared dopamine agonist in combination with co-intervention with co-intervention and 10 trials compared dopamine agonists with other active interventions (one trial compared DA with two other interventions). Overall, when compared with placebo or no intervention, dopamine agonists had a lower risk of developing moderate or severe OHSS without influencing pregnancy outcomes such as live birth rate for those women who proceeded to have a fresh embryo transfer, clinical pregnancy rate, multiple pregnancy rate, and miscarriage rate. However, data on the live birth rate were scarce or incomplete in the included trials.

There was an increased risk of adverse events, which occurred rarely and were mild, associated with dopamine agonists particularly when using quinagolide. Cabergoline was associated with a lower risk of moderate or severe OHSS, without influencing pregnancy outcomes when compared with placebo or no intervention. Quinagolide appeared to reduce the risk of moderate or severe OHSS, but might increase the incidence of adverse events, although the reported events were mainly very mild gastrointestinal and central nervous system symptoms, especially compared to the risks of severe OHSS. With the limited data available, bromocriptine did not influence the incidence of moderate or severe OHSS.

Dopamine agonist plus co-intervention may reduce the risk of moderate or severe OHSS compared to co-intervention alone. We are uncertain of the effect of dopamine agonist plus co-intervention and co-intervention in other outcomes of interest.

When compared with other active interventions, we reported OHSS data in subgroups per type of intervention, due to large heterogeneity across subgroups. When compared with human albumin and coasting, cabergoline might reduce the incidence of moderate or severe OHSS, but dopamine agonists might increase that risk compared to diosmin. We are uncertain of an effect on OHSS rates when comparing cabergoline to other active interventions such as prednisolone or HES or calcium gluconate infusion. Also, we were uncertain of any effect on pregnancy outcomes and adverse events when comparing cabergoline versus other active interventions.

The quality of the evidence for the comparison of dopamine agonist with placebo/no intervention was moderate but for the other comparators the evidence was low or very low. The main limitations causing these quality judgements were poor reporting of study methods (mostly lack of details on randomisation and blinding), heterogeneity across trials, and risk of imprecision (low number of events or small sample sizes).

Overall completeness and applicability of evidence

Compared with the previous published version of this review (Tang 2016), we included six additional trials. In total, this updated Cochrane Review included 22 trials involving 3171 women at high risk of OHSS. The study populations varied among trials regarding the definition of 'women at high risk' of OHSS. This may influence the incidence of OHSS and limits the applicability of study results in practice. However, as some trials even excluded the truly 'high risk of OHSS' women from participating, we do not know whether this effect of dopamine agonists could also be seen when these women were not excluded. Most of the trials defined moderate or severe OHSS according to Golan's classification (Golan 1989), but five trials used other definitions (undefined, or following the criteria defined by Mathur and colleagues (Mathur 2007) or Humaidan and colleagues (Humaidan 2010). This may induce bias when pooling the data of the various studies. Only a few studies reported pregnancy outcomes such as live birth. The influence of dopamine agonists on pregnancy outcomes requires further study; however, many units will practice an embryo 'freeze-all' approach for women at risk of OHSS and, therefore, data for pregnancy outcomes may not be forthcoming. Most of the trials evaluated the dopamine agonist cabergoline, whereas two trials evaluated quinagolide and one trial evaluated bromocriptine. In addition, our evidence was applicable in low- to middle-income countries as most trials were performed in these countries. Finally, due to the lack of studies comparing a dopamine agonist with another dopamine agonist, we were unable to determine which dopamine agonist is most effective in preventing OHSS.

Quality of the evidence

The methodological quality of the 22 included trials varied. Fifteen trials used correct random sequence generation, and only five trials had a low risk of bias in the domain of allocation concealment. Four trials were either single or double blind. One trial was at high risk of bias due to a high percentage of dropouts without reported reasons (Beltrame 2013). All trials reported the outcomes of OHSS, but only six studies provided the primary outcome of 'live birth rate.' See Figure 2 and Figure 3 for the 'Risk of bias' assessments of the included studies.

Moreover, the overall body of evidence for primary outcomes between dopamine agonist and placebo or no intervention was moderate. The main reasons for downgrading the quality of the evidence were: poor reporting of study methods (e.g. 36% of RCTs did not report the methods of allocation concealment or blinding) and risk of imprecision (e.g. low number of events). See Summary of findings 1; Summary of findings 2; and Summary of findings 3 for more details.

Potential biases in the review process

We tried to identify all eligible trials by conducting a systematic review of the literature without restrictions of publication type or language. Moreover, we contacted the authors of trials for more information about any unpublished data. For the missing participants who did not report the outcome, we assumed that the events did not occur.

Agreements and disagreements with other studies or reviews

Our results are in agreement with most of the systematic reviews and meta-analyses on dopamine agonists for the prevention for OHSS (Baumgarten 2013; Guo 2016; Kalampokas 2013; Kasum 2014; Leitao 2014; Youssef 2010). The first systematic review published in 2010 included only four RCTs with 570 women, and showed that cabergoline might reduce the incidence of OHSS. However, it found no evidence of a reduction in severe OHSS

(Youssef 2010), which is consistent with our previous Cochrane Review (Tang 2016). This might be caused by a small sample size or low event rate of severe OHSS. In 2014, another systematic review included eight trials involving 858 women and showed that cabergoline could reduce the risk of moderate or severe OHSS, as well as severe OHSS (Leitao 2014). In 2016, one systematic review and network meta-analysis of 31 RCTs involving 7181 women showed that cabergoline was superior to placebo or human albumin, or glucocorticoid in decreasing OHSS incidence, and there was no evidence of a difference between cabergoline and other active interventions (e.g. aspirin, HES, calcium infusion or metformin). However, until 2016, few systematic reviews included types of dopamine agonist other than cabergoline. One systematic review showed that a dopamine agonist appeared to be effective for the prevention of OHSS (Baumgarten 2013). Moreover, there was no evidence of adverse effects on pregnancy outcomes (Baumgarten 2013; Leitao 2014; Youssef 2010). Compared with previous systematic reviews, our review includes more trials and women, and can, therefore, draw a more robust conclusion that the use of dopamine agonists could reduce the incidence of moderate or severe OHSS.

In future OHSS trials, it will probably be considered unethical to withhold women who are at risk of OHSS from having all their embryos frozen for replacement in a subsequent cycle, as current embryo survival rates after freezing are generally excellent and the transfer of a frozen embryo in an unstimulated cycle avoids the risk of OHSS in that cycle.

AUTHORS' CONCLUSIONS

Implications for practice

In women at high-risk of developing ovarian hyperstimulation syndrome (OHSS), dopamine agonists probably reduce the incidence of moderate or severe OHSS when compared to placebo/no intervention, based on moderate-quality evidence. The dopamine agonists cabergoline and quinagolide reduce the incidence of moderate or severe OHSS. There is very minimal evidence from one trial that bromocriptine does not reduce the incidence of moderate or severe OHSS. There is no evidence that cabergoline or quinagolide influence pregnancy outcomes such as live birth rate, clinical pregnancy rate, multiple pregnancy rate, and miscarriage rate. However, quinagolide might increase the incidence of adverse events, and we should, therefore, weigh the benefits and harms of this medication before starting treatment. In addition, some evidence suggests that a dopamine agonist plus other active intervention probably offer an additive benefit in the incidence of moderate or severe OHSS, but not other outcomes of interest when compared with other active intervention alone. When compared with other active interventions, we are uncertain of the effects of dopamine agonists on moderate or severe OHSS and clinical outcomes (e.g. pregnancy and adverse events).

Implications for research

Further research should consider the risks of dopamine agonists, compare different types of dopamine agonists with regard to clinical outcomes and safety profiles, compare different doses (lowest possible dose while safe-guarding the preventive effect) and duration of treatment, and investigate the potential role of bromocriptine in OHSS prevention. Moreover, comparisons with other treatments that have been proven effective (such as the use of gonadotropin-releasing hormone (GnRH) antagonist protocols or metformin in women with polycystic ovary syndrome (PCOS)) and the consideration of combination treatments should be studied to find the most effective strategy to prevent OHSS. Special attention should be paid to the definition of 'high-risk' women. Thus, large, well-designed, and well-executed randomised controlled trials (RCTs) that involve all clinical endpoints (i.e. moderate and severe OHSS, and if women were to proceed to a fresh embryo transfer; clinical pregnancy rate, miscarriage rate, ongoing pregnancy rate, live birth rate, and adverse events) are necessary to evaluate the promising role of dopamine agonists in OHSS prevention further.

Some of the studies in this review excluded women with very high oestradiol (E_2) levels, very early OHSS, or need for coasting and assigned those women to cycle cancellation and a 'freeze all' approach. Pregnancy results of these subsequent transfer cycles were – per review protocol – not included in this review. However, postponing an embryo transfer to a subsequent cycle might very well have a beneficial effect on both pregnancy outcomes and OHSS severity, as well as the incidence of late OHSS when no transfer or pregnancy would directly follow from the hyperstimulated oocyte-harvesting cycle. As higher success rates of cryopreserved embryo transfers are consistently being reported in the last years, a 'freeze all' approach has been suggested as the standard in ART, as it is hypothesised that a subsequent embryo transfer cycle is more beneficial for implantation chances. This paradigm shift might have a beneficial effect on OHSS rates and lessen the need for OHSS prevention strategies. Therefore, it would be interesting to study OHSS incidence in 'freeze all' cycles and follow up on their (cumulative) pregnancy data in subsequent transfer cycles.

ACKNOWLEDGEMENTS

We acknowledge the Cochrane Gynaecology and Fertility Group (formerly MDSG), especially the Information Specialist, Marian Showell, and Managing Editors, Helen Nagels and Editor Jane Marjoribanks. Thanks to Dr Amr Salah, Dr Farnaz Sohrabvand, Dr Wellington Martins, Dr Irina Fetisova, and Dr Rutvij Dalal for providing more detailed information on several trials.

The authors of the 2021 update thank Dr Tamara Hunter, Dr Yongfang Hu, and Dr Xiaoyan Sheng for their contributions to previous versions of this review. They thank also Dr Ruth Hodgson, Dr Shantini Paranjothy and Dr Vanessa Jordan for providing referee comment on the updated review.

REFERENCES

References to studies included in this review

Alhalabi 2011 *{published and unpublished data}*

Alhalabi M, Samawi S, Kafri N, Sharif J, Saker A, Othman A. Role of quinagolide (Norprolac) in preventing ovarian hyperstimulation syndrome (OHSS) in high risk intracytoplasmic sperm injection (ICSI) patients. *Fertility and Sterility* 2010;**98**(3 Suppl 1):S103.

Alhalabi M, Samawi S, Taha A, Kafri N, Modi S, Khatib A. Quinagolide reduces OHSS in high risk ICSI patients. *Human Reproduction* 2011;**26**(Suppl 1):P-508.

El-Shaer H, Fouda U, Hanafy A, Nabil H, Mehrem W. Cabergoline versus calcium gluconate infusion in the prevention of ovarian hyperstimulation syndrome. A randomized controlled trial. *Human Reproduction* 2019;**34**(1):i74.

Alvarez 2007a *{published data only}*

Alvarez C, Bosch E, Melo MA, Fernandez-Sanches M, Munoz EA, Remohi J, et al. The dopamine agonist cabergoline prevents moderate-severe early ovarian hyperstimulation syndrome (OHSS) in high-risk ART patients. *Human Reproduction* 2006;**21**:i96.

* Alvarez C, Martí-Bonmatí L, Novella-Maestre E, Sanz R, Gómez R, Fernández-Sánchez M, et al. Dopamine agonist cabergoline reduces hemoconcentration and ascites in hyperstimulated women undergoing assisted reproduction. *Journal of Clinical Endocrinology and Metabolism* 2007;**92**:2931-7.

Amir 2015 *{published and unpublished data}*

* Amir H, Yaniv D, Hasson J, Amit A, Gordon D, Azem F. Cabergoline for reducing ovarian hyperstimulation syndrome in assisted reproductive technology treatment cycles. A prospective randomized controlled trial. *Journal of Reproductive Medicine* 2015;**60**(1-2):48-54.

Amir H, Yaniv Kovalski D, Amit A, Azem F. Can dopamine agonist cabergoline reduce ovarian hyperstimulation syndrome in ART treatment cycles? A prospective randomized study. *Fertility and Sterility* 2011;**95**(4):S84.

Bassiouny 2018 *{published data only}*

Bassiouny Yasmin A, Dakhly Dina MR, Bayoumi Yomna A, Salaheldin Noha M, Gouda Hisham M, Hassan Ayman A. Randomized trial of combined cabergoline and coasting in preventing ovarian hyperstimulation syndrome during in vitro fertilization/intracytoplasmic sperm injection cycles. *International Journal of Gynaecology and Obstetrics* 2018;**140**(2):217-22.

Beltrame 2013 *{published and unpublished data}*

Beltrame AL, Serafini P, Motta EL, Soares JM Jr, Baracat EC. The effects of bromocriptine on VEGF, kidney function and ovarian hyperstimulation syndrome in in vitro fertilization patients: a pilot study. *Gynecological Endocrinology* 2013;**29**(3):201-4.

Busso 2010 *{published data only}*

Busso C, Fernandez-Sanchez M, Garcia-Velasco JA, Landeras J, Ballesteros A, Munoz E, et al. The non-ergot derived dopamine agonist quinagolide in prevention of early ovarian hyperstimulation syndrome in IVF patients: a randomized, double-blind, placebo-controlled trial. *Human Reproduction* 2010;**25**(4):995-1004.

Carizza 2008 *{published data only}*

* Carizza C, Abdelmassih V, Abdelmassih S, Ravizzini P, Salgueiro L, Salgueiro PT, et al. Cabergoline reduces the early onset of ovarian hyperstimulation syndrome: a prospective randomized study. *Reproductive Biomedicine Online* 2008;**17**:751-5.

Carizza C, Abdelmassih V, Ravizzini PC, Salgueiro LL. Ongoing clinical pregnancy is not affected by cabergoline use in women undergoing ICSI with estradiol levels beyond 4000 pg/ml on the day of the hCG. *Human Reproduction* 2008;**23**(Suppl 1):i141.

Dalal 2014 *{published and unpublished data}*

Dalal R, Mishra A. Comparison of coasting with cabergoline administration for prevention of early severe OHSS. *BJOG* 2014;**121**:78.

Elnory 2018 *{published data only}*

Elnory MA, Elmantwe AN. Comparison of cabergoline versus calcium infusion in ovarian hyperstimulation syndrome prevention: a randomized clinical trial. *Middle East Fertility Society Journal* 2018;**23**(4):357-62.

El-Shaer 2019 *{unpublished data only}*

El-Shaer H, Fouda U, Youssef G, Hanafy A, Nabil H, Mehrem W. Cabergoline versus calcium gluconate infusion in the prevention of ovarian hyperstimulation syndrome. A randomized controlled trial. *Human Reproduction* 2019;**34**:i74.

Fetisova 2014 *{published and unpublished data}*

Fetisova S, Korneeva I, Saroyan T, Krechetova L, Ivanets T. Effects of cabergoline administration for the prevention of OHSS upon the levels of VEGF, VEGFR-1 and VEGFR-2 in high risk IVF/ICSI patients. *Human Reproduction* 2014;**29**(Suppl 1):P-482.

Ghahiri 2015 *{published data only}*

* Ghahiri A, Mogharehabed N, Hosseini N. Evaluation of intravenous hydroxyethyl starch, intravenous albumin 20% and oral cabergoline for prevention of ovarian hyperstimulation syndrome in patients undergoing ovulation induction. *Journal of Research in Medical Sciences* 2015;**20**(7):693-6.

Ghahiri A, Mogharehabed N, Hosseini N. Evaluation of three different strategies (intravenous hydroxyl ethyl starch, intravenous albumin 20%, and oral cabergoline) for prevention of ovarian hyperstimulation syndrome in patients undergoing ovulation induction. *Iranian Journal of Reproductive Medicine* 2014;**12**(6):4.

Jellad 2017 *{published data only}*

Jellad S, Haj Hassine A, Basly M, Mrabet A, Chibani M, Rachdi R. Vascular endothelial growth factor antagonist reduces the early onset and the severity of ovarian hyperstimulation syndrome. Journal de Gynécologie, Obstétrique et Biologie de la Reproduction 2017;**46**(1):87-91.

Kilic 2015 *{published data only}*

Kilic N, Ozdemir O, Basar HC, Demircan F, Ekmez F, Yucel O. Cabergoline for preventing ovarian hyperstimulation syndrome in women at risk undergoing in vitro fertilization/ intracytoplasmic sperm injection treatment cycles: a randomized controlled study. *Avicenna Journal of Medicine* 2015;**5**:123-7.

Matorras 2013 *{published and unpublished data}*

Matorras R, Andres M, Mendoza R, Prieto B, Pijoan JI, Exposito A. Prevention of ovarian hyperstimulation syndrome in GnRH agonist IVF cycles in moderate risk patients: randomized study comparing hydroxyethyl starch versus cabergoline and hydroxyethyl starch. *European Journal of Obstetrics and Gynecology and Reproductive Biology* 2013;**170**(2):439-43.

Saad 2017 *{published data only}*

Saad AS, Mohamed KA. Diosmin versus cabergoline for prevention of ovarian hyperstimulation syndrome. *Middle East Fertility Society Journal* 2017;**22**(3):206-10.

Salah 2012 *{published data only}*

* Salah AM, El-Helew Y. Can cabergoline prevent ovarian hyperstimulation syndrome in polycystic ovarian patients undergoing gonadotropin stimulation? *Evidence Based Women's Health Journal* 2012;**2**(2):56-9.

Salah Edeen AM, Alhelou YM. Can cabergoline prevent ovarian hyperstimulation syndrome in PCO patients undergoing gonadotropin stimulation? Comparative study with prednisolone. *Human Reproduction* 2009;**24**(1):i60.

Shaltout 2012 *{published data only}*

Shaltout A, Shohayeb A, Eid M. Role of cabergoline in preventing ovarian hyperstimulation syndrome in high risk intracytoplasmic sperm injection (ICSI) patients and effect on outcome. *Human Reproduction* 2009;**24**(Suppl 1):O-154.

* Shaltout A, Shohayeb A, Youssef MA. Can dopamine agonist at a low dose reduce ovarian hyperstimulation syndrome in women at risk undergoing ICSI treatment cycles? A randomized controlled study. *European Journal of Obstetrics, Gynecology, and Reproductive Biology* 2012;**165**(2):254-8.

Singh 2017 *{published data only}*

Singh S, Raman AK, Ramakrishnan S, Mohamed Ashraf C. Efficacy of cabergoline in the prevention of ovarian hyperstimulation syndrome: a randomized, double-blind and placebo-controlled trial. *International Journal of Infertility and Fetal Medicine* 2017;**8**(2):54-60.

Sohrabvand 2009 *{published data only}*

Sohrabvand F, Ansaripour S, Bagheri M, Shariat M, Jafarabadi M. Cabergoline versus coasting in the prevention of ovarian hyperstimulation syndrome and assisted reproductive technologies outcome in high risk patients. *International Journal of Fertility and Sterility* 2009;**3**(1):35-40.

Tehraninejad 2012 *{published data only}*

Tehraninejad ES, Hafezi M, Arabipoor A, Aziminekoo E, Chehrazi M, Bahmanabadi A. Comparison of cabergoline and intravenous albumin in the prevention of ovarian hyperstimulation syndrome: a randomized clinical trial. *Journal of Assisted Reproduction and Genetics* 2012;**29**(3):259-64.

Torabizadeh 2013 *{published and unpublished data}*

Torabizadeh A, Vahidroodsari F, Ghorbanpour Z. Comparison of albumin and cabergoline in the prevention of ovarian hyperstimulation syndrome: a clinical trial study. *Iranian Journal of Reproductive Medicine* 2013;**11**(10):837-42.

References to studies excluded from this review

Aflatoonian 2008 *{published and unpublished data}*

Aflatoonian A, Ghandi S, Tabibnejad N. Comparison of coasting with cabergoline administration for prevention of early severe OHSS in ART cycles. *Iranian Journal of Reproductive Medicine* 2008;**6**(2):51-5.

Agha Hosseini 2010 *{published and unpublished data}*

Agha Hosseini M, Aleyasin A, Mahdavi A, Nezami R, Safdarian L, Fallahi P. Cabergoline for prevention of ovarian hyperstimulation syndrome in high risk patients. *Iranian Journal of reproductive Medicine* 2010;**8**:70.

Alvarez 2007b *{published data only}*

Alvarez C, Alonso-Muriel I, Garcia G, Crespo J, Bellver J, Simon C, et al. Implantation is apparently unaffected by the dopamine agonist cabergoline when administered to prevent ovarian hyperstimulation syndrome in women undergoing assisted reproduction treatment: a pilot study. *Journal of Clinical Endocrinology and Metabolism* 2007;**22**:3210-4.

Ata 2009 *{published data only}*

Ata B, Seyhan A, Orhaner S, Urman B. High dose cabergoline in management of ovarian hyperstimulation syndrome. *Fertility and Sterility* 2009;**92**(3):1168.e1-4.

Fouda 2016 *{published and unpublished data}*

Fouda UM, Sayed AM, Elshaer HS, Hammad BE, Shaban MM, Elsetohy KA, et al. GnRH antagonist rescue protocol combined with cabergoline versus cabergoline alone in the prevention of ovarian hyperstimulation syndrome: a randomized controlled trial. *Journal of Ovarian Research* 2016;**9**(1):29.

Ghaebi 2016 *{published data only}*

Ghaebi NK, Amirian M, Zarmehri B, Zabihi H. Comparison of the effect of letrozole versus cabergoline for prevention of ovarian hyperstimulation syndrome (OHSS) in patients under ovulation induction treatments and IVF cycles. *Iranian Journal of Obstetrics, Gynecology and Infertility* 2016;**18**(184):1-8.

Gualtieri 2011 *{published data only}*

Gualtieri M, Hoffman D, Barrionuevo M, Christie D, Mouhayar Y, Ory SJ. The effects of cabergoline on ovarian

hyperstimulation syndrome (OHSS) and pregnancy outcomes on in vitro fertilization (IVF) patients. *Fertility and Sterility* 2011;**95**(4):S259-60.

Guvendag 2010 *{published data only}*

Guvendag GE, Dilbaz S, Cinar O, Ozdegirmenci O, Aydin S. The effect of cabergoline on follicular microenvironment profile in patients with high risk of OHSS. *Fertility and Sterility* 2010;**94**(4):S180-1.

Hatton 2012 *{published data only}*

Hatton A, Parry S, Hughes G, Wallbutton S, Binnersley S, Lavender A, et al. Cabergoline does not appear to affect pregnancy rates in patients undergoing assisted reproduction. *Human Fertility* 2012;**15**(s1):16.

Hosseini 2011 *{published data only}*

Hosseini MA, Aleyasin A, Mahdavi A, Nezami R, Safdarian L, Fallahi P. The effectiveness of cabergoline for the prevention of ovarian hyperstimulation syndrome. *Iranian Journal of Medical Science* 2011;**36**(3):207-12.

Khan 2010 *{published data only}*

Khan Z, Rollene N, Amols M, Gada R, Coddington C. Cabergoline and ganirelix therapy for early moderate to severe ovarian hyperstimulation syndrome (OHSS) results in faster recovery than in early untreated OHSS. *Fertility and Sterility* 2010;**93**(5):S14.

Naredi 2013 *{published and unpublished data}*

Naredi N, Karunakaran S. Calcium gluconate infusion is as effective as the vascular endothelial growth factor antagonist cabergoline for the prevention of ovarian hyperstimulation syndrome. *Journal of Human Reproductive Sciences* 2013;**6**(4):248-52.

Rollene 2009a *{published data only}*

Rollene NL, Amols MH, Hudson SB, Coddington CC. Treatment of ovarian hyperstimulation syndrome using a dopamine agonist and gonadotropin releasing hormone antagonist: a case series. *Fertility and Sterility* 2009;**92**(3):1169.e15-7.

Rollene 2009b *{published data only}*

Rollene NL, Amols MH, Hudson SB, Jensen JR, Morbeck DE, Coddington CC. Cabergoline and ganirelix treatment of ovarian hyperstimulation syndrome (OHSS) results in rapid clinical improvement. *Fertility and Sterility* 2009;**92**(3):S240-1.

Saad 2016 *{published data only}*

Saad AS, Mohamed KA, Saad SA. Calcium dobesilate versus cabergoline for prevention of ovarian hyperstimulation syndrome. *Human Reproduction* 2016;**31**(Supp 1):P-580.

Saad 2019 *{published data only}*

Saad A, Eissa S, Abdellateef W. Diosmin addition to cabergoline for the prevention of OHSS, will it differ? A pilot study. *BJOG* 2019;**126**:200.

Seow 2013 *{published and unpublished data}*

Seow KM, Lin YH, Bai CH, Chen HJ, Hsieh BC, Huang LW, et al. Clinical outcome according to timing of cabergoline initiation for prevention of OHSS: a randomized controlled trial. *Reproductive Biomedicine Online* 2013;**26**(6):562-8.

Seyam 2018 *{published data only}*

Seyam E, Hefzy E. Laparoscopic ovarian drilling versus GnRH antagonist combined with cabergoline as a prophylaxis against the re-development of ovarian hyperstimulation syndrome. *Gynecological Endocrinology* 2018;**34**(7):616-22.

Sherwal 2010 *{published data only}*

Sherwal V, Malik S, Bhatia V. Effect of bromocriptine on the severity of ovarian hyperstimulation syndrome and outcome in high responders undergoing assisted reproduction. *Journal of Human Reproductive Sciences* 2010;**3**(2):85-90.

Soliman 2011 *{published data only}*

Soliman BS. Cabergoline vs intravenous albumin or combination of both for prevention of the early onset ovarian hyperstimulation syndrome. *Middle East Fertility Society Journal* 2011;**16**(1):56-60.

Spitzer 2011 *{published data only}*

Spitzer D, Wogatzky J, Murtinger M, Zech MH, Haidbauer R, Zech NH. Dopamine agonist bromocriptine for the prevention of ovarian hyperstimulation syndrome. *Fertility and Sterility* 2011;**95**(8):2742-4.e1.

Zahran 2018 *{published data only}*

Zahran KM, Mostafa WA, Abbas AM, Khalifa MA, Sayed GH. Clomiphene citrate plus cabergoline versus clomiphene citrate for induction of ovulation in infertile euprolactinemic patients with polycystic ovary syndrome: a randomized clinical trial. *Middle East Fertility Society Journal* 2018;**23**(3):173-7.

Zargar 2011 *{published data only}*

Zargar M, Nikbakht R, Pourmatroud E, Ghasemi K, Hemadi M. Comparison of the clinical efficacy of two different cabergoline regimens on prevention of ovarian hyperstimulation syndrome (OHSS). *Research Journal of Obstetrics and Gynecology* 2011;**4**(2):51-8.

References to studies awaiting assessment

Ahmadi 2010 *{published data only}*

Ahmadi S, Rahmani E, Oskouian H. Cabergoline versus human albumin in prophylaxis of ovarian hyperstimulation syndrome. *Reproductive Biomedicine Online* 2010;**20**:S41.

Ahmadi SH, Rahmani E, Oskouian H. Cabergoline versus human albumin in prophylaxis of ovarian hyperstimulation syndrome. *Iranian Journal of Reproductive Medicine* 2011;**9**(Suppl 1):6 Abstract O-13.

References to ongoing studies

El Khattan 2015 *{published and unpublished data}*

Comparative study between cabergoline and intravenous calcium in the prevention of ovarian hyperstimulation in women with polycystic ovarian disease undergoing

intracytoplasmic sperm injection (ICSI). Ongoing study. July 2013. Contact author for more information.

Hendricks 2015 *{published and unpublished data}*

Study of cabergoline for prevention of ovarian hyperstimulation syndrome (OHSS) in in vitro fertilization cycles and derivation of OHSS biomarkers. Ongoing study. 15 February 2012. Contact author for more information.

IRCT2016071428930N1 *{unpublished data only}*

Effects of calcium in the prevention of ovarian hyperstimulation syndrome in patients undergoing IVF/ICSI. Ongoing study. 1 April 2016. Contact author for more information.

Kamel 2015 *{published and unpublished data}*

Effect of cabergoline on endometrial vascularity during intracytoplasmic sperm injection. Ongoing study. December 2014. Contact author for more information.

Khaled 2014 *{unpublished data only}*

Diosmin versus cabergoline for prevention of ovarian hyperstimulation syndrome (infertility). Ongoing study. May 2014. Contact author for more information.

Additional references

Aboulghar 2003

Aboulghar MA, Mansour RT. Ovarian hyperstimulation syndrome: classifications and critical analysis of preventive measures. *Human Reproduction Update* 2003;**9**(3):275-89.

Aboulghar 2009

Aboulghar M. Symposium: update on prediction and management of OHSS – prevention of OHSS. *Reproductive Biomedicine Online* 2009;**19**(1):33-42.

Al-Inany 2011

Al-Inany H, Youssef M, Aboulghar M, Broekmans F, Sterrenburg M, Smit J, et al. Gonadotrophin-releasing hormone antagonists for assisted reproductive technology. *Cochrane Database of Systematic Reviews* 2011, Issue 5. Art. No: CD001750. [DOI: 10.1002/14651858.CD001750.pub3]

Baumgarten 2013

Baumgarten M, Polanski L, Campbell B, Raine-Fenning N. Do dopamine agonists prevent or reduce the severity of ovarian hyperstimulation syndrome in women undergoing assisted reproduction? A systematic review and meta-analysis. *Human Fertility (Cambridge)* 2013;**16**(3):168-74.

Budayr 2020

Budayr A, Tan TC, Lo JC, Zaroff JG, Tabada GH, Yang J, et al. Cardiac valvular abnormalities associated with use and cumulative exposure of cabergoline for hyperprolactinemia: the CATCH study. *BMC Endocrine Disorders* 2020;**20**:25.

Busso 2009

Busso CE, Garcia-Velasco J, Gomez R, Alvarez C, Simon C, Pellicer A. Symposium: update on prediction and management of OHSS: prevention of OHSS – dopamine agonists. *Reproductive Biomedicine Online* 2009;**19**(1):43-51.

Casper 2015

Casper RF. Reducing the risk of OHSS by GnRH agonist triggering. *Journal of Clinical Endocrinology and Metabolism* 2015;**100**(12):4396-8.

Castelo-Branco 2009

Castelo-Branco C, Del Pino M, Valladares E. Ovarian hyperstimulation, hyperprolactinaemia and LH gonadotroph adenoma. *Reproductive Biomedicine Online* 2009;**19**(2):153-5.

CGF

Cochrane Gynaecology and Fertility Group. CGF guidance for writing all sections of systematic reviews. https://cgf.cochrane.org/sites/cgf.cochrane.org/files/public/uploads/cgf_guidance_15_oct_2020.pdf (accessed 9 March 2021).

Costello 2012

Costello MF, Misso ML, Wong J, Hart R, Rombauts L, Melder A, et al. Treatment of infertility in polycystic ovary syndrome: a brief update. *Australian & New Zealand Journal of Obstetrics & Gynaecology* 2012;**52**(4):400-3.

D'Angelo 2007

D'Angelo A, Amso NN. Embryo freezing for preventing ovarian hyperstimulation syndrome. *Cochrane Database of Systematic Reviews* 2007, Issue 3. Art. No: CD002806. [DOI: 10.1002/14651858.CD002806.pub2]

D'Angelo 2017

D'Angelo A, Amso NN, Hassan R. Coasting (withholding gonadotrophins) for preventing ovarian hyperstimulation syndrome. *Cochrane Database of Systematic Reviews* 2017, Issue 5. Art. No: CD002811. [DOI: 10.1002/14651858.CD002811]

Delvigne 2002

Delvigne A, Rozenberg S. A qualitative systematic review of coasting, a procedure to avoid ovarian hyperstimulation syndrome in IVF patients. *Human Reproduction Update* 2002;**18**(3):291-6.

Edwards 2007

Edwards RG. IVF, IVM, natural cycle IVF, minimal stimulation IVF – time for a rethink. *Reproductive Biomedicine Online* 2007;**15**(1):106-19.

Glade-Bender 2003

Glade-Bender J, Kandel JJ, Yamashiro DJ. VEGF blocking therapy in the treatment of cancer. *Expert Opinion on Biological Therapy* 2003;**3**:263-76.

Golan 1989

Golan A, Ron-el R, Herman A, Soffer Y, Weinraub Z, Caspi E. Ovarian hyperstimulation syndrome: an update review. *Obstetrical & Gynecological Survey* 1989;**44**(6):430-40.

Gómez 2002

Gómez R, Simon C, Remohi J, Pellicer A. Vascular endothelial growth factor receptor-2 activation induces

vascular permeability in hyperstimulated rats, and this effect is prevented by receptor blockade. *Endocrinology* 2002;**143**:4339-48.

Gómez 2006

Gómez R, González-Izquierdo M, Zimmermann RC, Novella-Maestre E, Alonso-Muriel I, Sanchez-Criado J, et al. Low-dose dopamine agonist administration blocks vascular endothelial growth factor (VEGF)-mediated vascular hyperpermeability without altering VEGF receptor 2-dependent luteal angiogenesis in a rat ovarian hyperstimulation model. *Endocrinology* 2006;**147**:5400-11.

GRADEpro GDT 2015

GRADE Working Group, McMaster University. GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. gradepro.org (accessed 9 October 2020).

Guo 2016

Guo JL, Zhang DD, Zhao Y, Zhang D, Zhang XM, Zhou CQ, et al. Pharmacologic interventions in preventing ovarian hyperstimulation syndrome: a systematic review and network meta-analysis. *Scientific Reports* 2016;**6**:19093.

Higgins 2011

Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from training.cochrane.org/handbook/archive/v5.1/.

Higgins 2019

Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6 (updated July 2019). Cochrane, 2019. Available from training.cochrane.org/handbook/archive/v6.

Humaidan 2010

Humaidan P, Quartarolo J, Papanikolaou EG. Preventing ovarian hyperstimulation syndrome: guidance for the clinician. *Fertility and Sterility* 2010;**94**(2):389-400.

Kalampokas 2013

Kalampokas T, Creatsas G, Kalampokas E. Cabergoline as treatment of ovarian hyperstimulation syndrome: a review. *Gynecological Endocrinology* 2013;**29**(2):98-100.

Kars 2008

Kars M, Delgade V, Holman ER, Feelders RA, Smit JW, Romijn JA, et al. Aortic valve calcification and mild tricuspid regurgitation but no clinical heart disease after 8 years of dopamine agonist therapy for prolactinoma. *Journal of Clinical Endocrinology and Metabolism* 2008;**93**(9):3348-56.

Kasum 2014

Kasum M, Vrčić H, Stanić P, Ježek D, Orešković S, Beketić-Orešković L, et al. Dopamine agonists in prevention of ovarian hyperstimulation syndrome. *Gynecological Endocrinology* 2014;**30**(12):845-9.

Knoepfelmacher 2006

Knoepfelmacher M, Danilovic DL, Rosa Nasser RH, Mendonca BB. Effectiveness of treating ovarian hyperstimulation syndrome with cabergoline in two patients with gonadotropin-producing pituitary adenomas. *Fertility and Sterility* 2006;**86**(3):719 e15-8.

Kuenen 2003

Kuenen BC, Tabernero J, Baselga J, Cavalli F, Pfanner E, Conte PF, et al. Efficacy and toxicity of the angiogenesis inhibitor SU5416 as a single agent in patients with advanced renal cell carcinoma, melanoma, and soft tissue sarcoma. *Clinical Cancer Research* 2003;**9**:1648-55.

Leitao 2014

Leitao V, Moroni R, Seko L, Nastri C, Martins W. Cabergoline for the prevention of ovarian hyperstimulation syndrome: a systematic review and meta-analysis of randomized controlled trials. *Fertility and Sterility* 2014;**101**(3):664-75.

Manno 2005

Manno M, Tomei F, Marchesan E, Adamo V. Cabergoline: a safe, easy, cheap, and effective drug for prevention/treatment of ovarian hyperstimulation syndrome? *European Journal of Obstetrics, Gynecology, and Reproductive Biology* 2005;**122**(1):127-8.

Martin 2009

Martin NM, Tan T, Meeran K. Dopamine agonists and hyperprolactinaemia. *BMJ* 2009;**338**:b381.

Mathur 2007

Mathur R, Kailasam C, Jenkins J. Review of the evidence base of strategies to prevent ovarian hyperstimulation syndrome. *Human Fertility* 2007;**10**(2):75-85.

Pauli 2005

Pauli SA, Tang H, Wang J, Bohlen P, Posser R, Hartman T, et al. The vascular endothelial growth factor (VEGF)/VEGF receptor 2 pathway is critical for blood vessel survival in corpora lutea of pregnancy in the rodent. *Endocrinology* 2005;**146**:1301.

Prakash 2009

Prakash A, Karasu T, Mathur R. Ovarian hyperstimulation syndrome: pathophysiology, prevention and management. *Obstetrics, Gynaecology and Reproductive Medicine* 2009;**19**(9):274-52.

Rabau 1967

Rabau E, David A, Serr DM, Mashiach S, Lunenfeld B. Human menopausal gonadotropins for anovulation and sterility. Results of 7 years of treatment. *American Journal of Obstetrics and Gynecology* 1967;**98**(1):92-8.

RCOG 2006

Royal College of Obstetricians and Gynaecologists (RCOG). The management of ovarian hyperstimulation syndrome. London (UK): Royal College of Obstetricians and Gynaecologists (RCOG). Green-top Guideline No 5 2006.

Review Manager 2014 [Computer program]

Nordic Cochrane Centre, The Cochrane Collaboration Review Manager (RevMan). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Rockwell 2002

Rockwell LC, Pillai S, Olson CE, Koos RD. Inhibition of vascular endothelial growth factor/vascular permeability factor action blocks estrogen-induced uterine edema and implantation in rodents. *Biology of Reproduction* 2002;**67**:1804-10.

Schade 2007

Schade R, Andershon S, Suissa S, Haverkamp W, Garbe E. Dopamine agonists and the risk of cardiac-valve regurgitation. *New England Journal of Medicine* 2007;**356**:29-38.

Soares 2008

Soares SR, Gomez R, Simon C, Garcia-Velasco JA, Pellicer A. Targeting the vascular endothelial growth factor system to prevent ovarian hyperstimulation syndrome. *Human Reproduction Update* 2008;**14**(4):321-3.

Soares 2012

Soares SR. Etiology of OHSS and use of dopamine agonists. *Fertility and Sterility* 2012;**97**(3):517-22.

Trifiro 2012

Trifiro G, Mokhles MM, Dieleman JP, van Soest EM, Verhamme K, Mazzaglia G, et al. Risk of cardiac valve regurgitation with dopamine agonist use in Parkinson's disease and hyperprolactinaemia: a multi-country, nested case-control study. *Drug Safety* 2012;**35**:159-71.

Tso 2014

Tso L, Costello M, Albuquerque L, Andriolo R, Macedo C. Metformin treatment before and during IVF or ICSI in women with polycystic ovary syndrome. *Cochrane Database of Systematic Reviews* 2014, Issue 11. Art. No: CD006105. [DOI: 10.1002/14651858.CD006105.pub3]

van der Linden 2015

van der Linden M, Buckingham K, Farquhar C, Kremer JA, Metwally M. Luteal phase support for assisted reproduction cycles. *Cochrane Database of Systematic Reviews* 2015, Issue 7. Art. No: CD009154. [DOI: 10.1002/14651858.CD009154.pub3]

Vloeberghs 2009

Vloeberghs V, Peeraer K, Pexsters A, D'Hooghe T. Ovarian hyperstimulation syndrome and complications of ART. *Best Practice & Research. Clinical Obstetrics & Gynaecology* 2009;**23**(5):691-709.

Walls 2012

Walls M, Junk S, Ryan JP, Hart R. IVF versus ICSI for the fertilization of in-vitro matured human oocytes. *Reproductive Biomedicine Online* 2012;**25**(6):603-7.

Walls 2015

Walls ML, Hunter T, Ryan JP, Keelan JA, Nathan E, Hart RJ. In vitro maturation as an alternative to standard in vitro fertilization for patients diagnosed with polycystic ovaries: a comparative analysis of fresh, frozen and cumulative cycle outcomes. *Human Reproduction* 2015;**30**(1):88-96.

Youssef 2010

Youssef MA, van Wely M, Hassan MA, Al-Inany HG, Mochtar M, Khattab S, et al. Can dopamine agonists reduce the incidence and severity of OHSS in IVF/ICSI treatment cycles? A systematic review and meta-analysis. *Human Reproduction Update* 2010;**16**(5):459-66.

Youssef 2016

Youssef MA, Mourad S. Volume expanders for the prevention of ovarian hyperstimulation syndrome. *Cochrane Database of Systematic Reviews* 2016, Issue 8. Art. No: CD001302. [DOI: 10.1002/14651858.CD001302]

Zanettini 2007

Zanettini R, Antonini A, Gatto G, Gentile R, Tesei S, Pezzoli G. Valvular heart disease and the use of dopamine agonists for Parkinson's disease. *New England Journal of Medicine* 2007;**356**:39-46.

References to other published versions of this review

Tang 2016

Tang H, Mourad S, Zhai SD, Hart RJ. Dopamine agonists for preventing ovarian hyperstimulation syndrome. *Cochrane Database of Systematic Reviews* 2016, Issue 11. Art. No: CD008605. [DOI: 10.1002/14651858.CD008605.pub3]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Alhalabi 2011

Study characteristics	
Methods	Randomised controlled prospective study
	No details on randomisation
	Quinagolide vs no drugs

Alhalabi 2011 *(Continued)*

	Setting: Syria
Participants	272 high-risk women undergoing ICSI with long protocol using GnRHa, $E_2 \geq 4000$ pg/mL on day of hCG, ≥ 20 follicles ≥ 10 mm in diameter Quinagolide group: 136 women Control group: 136 women June 2007 to January 2010
Interventions	Quinagolide group: quinagolide (Norprolac) 150 mg/day from the day of hCG administration for 15 days (6/136 (4.41%) women developed OHSS) Control group: no drugs (126/136 (9.12%) women developed OHSS)
Outcomes	OHSS symptoms assessed according to Golan's classification system, 4, 8, and 12 days after hCG administration Incidence of OHSS (quinagolide group vs control group): 6/136 vs 26/136 Live birth rate: not stated Miscarriage rate: not stated Clinical pregnancy rate: not stated, numbers reported as "similar rates" Multiple pregnancy rate: not stated Any other adverse effects of the treatment: not stated
Notes	2 different abstracts: in the *Human Reproduction* abstract: control group = 98 women, in the *Fertility and Sterility* abstract: control group = 136 women. This difference made it at risk for improper randomisation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly divided into two groups."
Allocation concealment (selection bias)	Unclear risk	Lack of sufficient information to permit judgement; only abstract available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Lack of sufficient information to permit judgement; only abstract available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Lack of sufficient information to permit judgement; only abstract available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Lack of sufficient information to permit judgement; only abstract available.
Selective reporting (reporting bias)	Unclear risk	Lack of sufficient information to permit judgement; only abstract available. No reporting on adverse effects or tolerability.

Alhalabi 2011 *(Continued)*

Other bias	Unclear risk	Lack of sufficient information to permit judgement; only abstract available. 2 different abstracts with different control group size, suggesting improper randomisation.

Alvarez 2007a

Study characteristics

Methods	Parallel design, single-centre randomised controlled trial Computer-based randomisation Cabergoline vs placebo Setting: Spain
Participants	82 oocytes donors, high-risk women with development of 20–30 follicles > 12 mm in diameter and retrieval of > 20 oocytes Exclusion criterion: coasting Cabergoline group: 41 women, only 35 women remained, because 6 women were discarded for < 20 oocytes retrieved Control group: 41 women, only 32 women remained, because 7 women were discarded for < 20 oocytes retrieved and 2 donors decided to withdraw No differences between groups in age or BMI; did not report the duration of infertility and causes of infertility
Interventions	Cabergoline group: cabergoline tablet 0.5 mg/day for 8 days from the day of hCG injection Control group: placebo tablet daily for 8 days
Outcomes	Moderate and severe OHSS identified by the modified classification of Golan and colleagues (Golan 1989) • Severe OHSS (cabergoline group vs control group): 4/41 vs 6/41 • Moderate OHSS (cabergoline group vs control group): 7/41 vs 14/41 Live birth rate: not stated Miscarriage rate: not stated Clinical pregnancy rate (cabergoline group vs control group): 16/41 vs 16/41 Multiple pregnancy rate: not stated Any other adverse effects of the treatment (cabergoline group vs control group): 8/41 vs 4/41 (adverse effects)
Notes	Supported by Grant SAF2004-06028 from Spanish Government

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The patients were allocated into two groups based on a computer randomization."

Alvarez 2007a *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Lack of sufficient information to permit judgement.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Assessor and participants blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessor and participants blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "thirteen patients discarded for not meeting the inclusion criteria and two donors decided to withdraw."
Selective reporting (reporting bias)	Unclear risk	No exclusions (no live birth rate mentioned).
Other bias	Unclear risk	Lack of sufficient information to permit judgement.

Amir 2015

Study characteristics	
Methods	Parallel design, single-centre, randomised controlled trial Computer-based randomisation Cabergoline vs no intervention Setting: Israel
Participants	40 high-risk women undergoing IVF/ET or IVF-PGD, aged 18–40 years, serum E_2 > 4000 pg/mL or the development of > 20 follicles > 12 mm in diameter Exclusion criteria: systemic disease and participating in other research studies Cabergoline group: 20 women Control group: 20 women
Interventions	Cabergoline group: cabergoline tablet 0.5 mg/day for 8 days from the day of hCG injection Control group: no cabergoline
Outcomes	Moderate and severe OHSS identified by the modified classification of Golan and colleagues (Golan 1989) assessed at day of ET, ET+7, ET+12 • Severe OHSS (cabergoline group vs control group): 0/20 vs 2/20 • Moderate OHSS (cabergoline group vs control group): 3/20 vs 10/20 Live birth rate: not reported Miscarriage rate (cabergoline group vs control group): 0/20 vs 1/20 Clinical pregnancy rate (fetal heartbeat) (cabergoline group vs control group): 2/20 vs 5/20 Multiple pregnancy rate (cabergoline group vs control group): 0/20 vs 1/20

Amir 2015 *(Continued)*

	Any other adverse effects of the treatment: not stated
Notes	Did apply coasting to both groups in about 50% of women if serum E_2 > 5000 pg/mL

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers.
Allocation concealment (selection bias)	Unclear risk	Lack of sufficient data to permit judgement.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Neither participants nor physicians blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Ultrasound experts were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data.
Selective reporting (reporting bias)	Unclear risk	No exclusions (no live birth rate mentioned).
Other bias	Unclear risk	Lack of sufficient data to permit judgement.

Bassiouny 2018

Study characteristics

Methods	Parallel, single-centre randomised controlled trial Block randomisation Cabergoline + coasting vs cabergoline vs coasting Setting: Egypt
Participants	300 high-risk women undergoing IVF or ICSI, aged 20–35 years, BMI ≤ 30 kg/m^2, had long GnRHa protocol treatment cycles, serum E_2 ≥ 3500 pg/mL on day of hCG administration, and had > 15 oocytes collected on ovum pick-up day Exclusion criteria: people with infertility due to male and uterine factors Cabergoline + coasting group: 100 women, 20 cancelled due to OHSS Cabergoline group: 100 women, 12 women cancelled due to OHSS Coasting group: 100 women, 4 women cancelled due to OHSS
Interventions	Cabergoline + coasting group: stopped receiving hMG for 1 day while continuing agonist injections and received cabergoline 0.25 mg/day for 8 days from hCG administration

Bassiouny 2018 *(Continued)*

	Cabergoline group: cabergoline 0.25 mg/day during IVF/ICSI cycle for 8 days following hCG administration Coasting group: stop receiving hMG for 1–3 days until safe E_2 levels were obtained; agonist injections continued
Outcomes	Incidence of OHSS classified by Golan and colleagues (Golan 1989) • Severe OHSS (cabergoline + coasting vs cabergoline vs coasting): 1/100 vs 1/100 vs 3/100 • Moderate OHSS (cabergoline + coasting vs cabergoline vs coasting): 1/100 vs 2/100 vs 6/100 • Moderate or severe OHSS (cabergoline + coasting vs cabergoline vs coasting): 2/100 vs 3/100 vs 9/100 Live birth rate (cabergoline + coasting vs cabergoline vs coasting): 48/100 vs 41/100 vs 40/100 Miscarriage rate: not stated Clinical pregnancy rate (cabergoline + coasting vs cabergoline vs coasting): 56/100 vs 49/100 vs 46/100 Multiple pregnancy rate: not stated Any other adverse effects of the treatment: not stated
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Used QuickCalcs to perform a block randomisation, with a block size of 4, to generate group assignments to 3 groups.
Allocation concealment (selection bias)	Low risk	Assignments were concealed in sealed opaque envelopes until enrolment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Both patients and investigators were unmasked to group assignments at enrolment.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Both patients and investigators were unmasked to group assignments at enrolment.
Incomplete outcome data (attrition bias) All outcomes	High risk	The reasons for cancellation were reported; however, a significant number of cycles (20+12+4) were cancelled due to OHSS, so the real severe OHSS cases were excluded.
Selective reporting (reporting bias)	Low risk	Most of outcomes were evaluated.
Other bias	Unclear risk	Lack of sufficient information to permit judgement.

Beltrame 2013

Study characteristics	
Methods	Multicentre, prospective, randomised, double-blind, placebo-controlled study

Beltrame 2013 *(Continued)*

	3 clinics Bromocriptine vs folic acid Setting: Brazil
Participants	47 women aged < 38 years undergoing IVF with ≥ 20 follicles as assessed by transvaginal ultrasound and E_2 > 3000 pg/mL on day prior to hCG administration Exclusion criteria: hyperprolactinaemia; use of dopaminergic agents or other medications for the treatment of hyperprolactinaemia or pituitary tumours; systemic diseases, such as arterial hypertension, hypotension, orthostatic hypotension, cardiovascular disease, and diabetes mellitus; polycystic ovaries Bromocriptine group: 23 women, 12/23 dropped out Folic acid group: 24 women, 7/24 dropped out
Interventions	Bromocriptine group: bromocriptine 2.5 mg/day continued for 14 days Folic acid group (placebo): folic acid 2.0 mg/day continued for 14 days Capsules same appearance and form
Outcomes	Incidence of OHSS (subgroups mild, moderate, severe), VEGF levels, urinary function Moderate and severe OHSS according to its OHSS criteria • Severe OHSS (bromocriptine group vs control group): 1/23 vs 6/24 • Moderate OHSS (bromocriptine group vs control group): 3/23 vs 4/24 • Total OHSS (bromocriptine group vs control group): 4/23 vs 10/24 Live birth rate: not stated Miscarriage rate: not stated Clinical pregnancy rate: not stated Multiple pregnancy rate: not stated Any other adverse effects of the treatment: not stated
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated using a random number generation algorithm.
Allocation concealment (selection bias)	Unclear risk	Lack of information to permit a judgement.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind; medication and folic acid as a placebo in same appearance capsules.
Blinding of outcome assessment (detection bias)	Unclear risk	Lack of information to permit a judgement.

Beltrame 2013 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	High risk	High dropout numbers without dropout analysis.
Selective reporting (reporting bias)	Unclear risk	No exclusions (no live birth rate mentioned).
Other bias	Unclear risk	Lack of information to permit a judgement.

Busso 2010

Study characteristics	
Methods	Randomised, parallel, double-blind randomised controlled trial Quinagolide vs placebo Setting: Spain
Participants	182 women undergoing IVF and ICSI treatment and at risk of developing OHSS with ≥ 20 follicles ≥ 10 mm on day of hCG administration Exclusion criteria: > 30 follicles or serum E_2 > 6000 pg/mL (or both) had cycle cancellation, previous coasting in this cycle, any clinically significant systemic disease, endocrine or metabolic abnormalities (pituitary, adrenal, pancreas, liver, or kidney), history of recurrent miscarriage, undiagnosed vaginal bleeding Quinagolide 50 µg group: 51 women Quinagolide 100 µg group: 52 women Quinagolide 200 µg group: 26 women Control group: 53 women
Interventions	4 tablets for every woman (combination of placebo/quinagolide 50 µg) Quinagolide 50 µg group: quinagolide 50 µg + 3 placebo tablets once daily, continuing until day before serum hCG test which took place 17+2 days after oocyte retrieval Quinagolide 100 µg group: quinagolide 100 µg + 2 placebo tablets once daily, continuing until day before serum hCG test which took place 17+2 days after oocyte retrieval Quinagolide 200 µg group: quinagolide 200 µg + no placebo tablets once daily, continuing until day before serum hCG test which took place 17+2 days after oocyte retrieval Control group: 4 placebo tablets once daily, continuing until day before serum hCG test which took place 17+2 days after oocyte retrieval
Outcomes	Moderate and severe OHSS identified by the modified classification of Golan and colleagues (Golan 1989) • Moderate/severe OHSS (quinagolide 50 µg group vs quinagolide 100 µg group vs quinagolide 200 µg group vs placebo group): 6/51 vs 7/52 vs 1/26 vs 12/53 Live birth rate (quinagolide 50 µg group vs quinagolide 100 µg group vs quinagolide 200 µg group vs placebo group): 23/51 vs 29/52 vs 14/26 vs 27/53

Busso 2010 *(Continued)*

	Miscarriage rate: not stated Clinical pregnancy rate (quinagolide 50 µg group vs quinagolide 100 µg group vs quinagolide 200 µg group vs placebo group): 22/51 vs 26/52 vs 11/26 vs 27/53 Multiple pregnancy rate: not stated Discontinued because of adverse events (quinagolide 50 µg group vs quinagolide 100 µg group vs quinagolide 200 µg group vs placebo group): 3/51 vs 7/52 vs 7/26 vs 0/53 Any other adverse effects of the treatment: nausea, dizziness, somnolence, diarrhoea, vomiting, lower abdominal pain, headache, abdominal distension, flatulence, upper abdominal pain, syncope
Notes	Sponsored by Ferring Pharmaceuticals WHO registry reference: EUCTR2006-000415-15-ES

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list prepared for each centre by a statistician not involved in the trial, and based on this the clinics were provided with individual code envelopes that were sealed to conceal the treatment group allocation.
Allocation concealment (selection bias)	Low risk	Computer-generated randomisation list provided to the clinics with individual code envelopes that were sealed to conceal the treatment group allocation. Block size was not disclosed.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind (participants, staff, and trial sponsor). All participants received 4 tablets (medication or placebo, or both).
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Lack of information to permit a judgement.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Systematic OHSS evaluation performed; high-dose arm stopped after poor tolerability of high-dose medication.
Selective reporting (reporting bias)	Low risk	Most of outcomes were evaluated.
Other bias	High risk	Poor tolerability of high dose could have revealed allocated group. Sponsored by Ferring Pharmaceuticals. Very high-risk women (> 30 follicles or serum E_2 > 6000 pg/mL, or both) excluded and underwent cycle cancellation.

Carizza 2008

Study characteristics

Methods	Parallel, single-centre randomised controlled trial

Carizza 2008 *(Continued)*

	Computer-based randomisation Cabergoline vs no intervention Setting: Brazil
Participants	166 women undergoing IVF and ICSI treatment and at risk of developing OHSS, defined as serum E_2 > 4000 pg/mL on day of hCG administration Exclusion criteria: not stated Cabergoline group: 83 women Control group: 83 women, 3 women were withdrawn for not completing the follow-up tests No differences between groups in age or BMI Did not report the duration of infertility and causes of infertility
Interventions	All participants received routine preventive IV HA 20 g on day of oocyte retrieval Cabergoline group: cabergoline 0.5 mg/day for 3 weeks from the day after oocyte retrieval Control group: no intervention
Outcomes	Moderate and severe OHSS identified by the modified classification of Golan and colleagues (Golan 1989) • Severe OHSS (cabergoline group vs control group): 2/83 vs 1/83 • Moderate OHSS (cabergoline group vs control group): 7/83 vs 14/83 Live birth rate: not stated Miscarriage rate (cabergoline group vs control group): 1/83 vs 3/83 Clinical pregnancy rate (cabergoline group vs control group): 33/83 vs 32/83 Multiple pregnancy rate (cabergoline group vs control group): multiple pregnancies were documented in all the severe cases of OHSS in both groups (2/83 vs 1/83) Any other adverse effects of the treatment: not stated
Notes	Authors reported no financial or commercial conflicts of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-based randomisation.
Allocation concealment (selection bias)	Unclear risk	Lack of sufficient information to permit judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Lack of sufficient information to permit judgement.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Lack of sufficient information to permit judgement.

Carizza 2008 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	3/200 women in control group could not complete their follow-up.
Selective reporting (reporting bias)	Unclear risk	No exclusions (no live birth rate mentioned).
Other bias	Unclear risk	Lack of sufficient information to permit judgement.

Dalal 2014

Study characteristics	
Methods	Single-centre randomised controlled trial Computer-based randomisation by independent research assistant Cabergoline vs coasting Setting: India
Participants	60 women undergoing IVF or ICSI cycles and at risk of developing OHSS, defined as the presence of preovulatory follicles ≥ 20 in both ovaries and E_2 ≥ 2500 pg/mL Exclusion criteria: not stated Cabergoline group: 30 women Coasting group: 30 women
Interventions	Cabergoline group: cabergoline 0.5 mg/day orally from the day of hCG for 8 days Coasting group: gonadotropins were withheld (while GnRHa was maintained), until the serum E_2 started to decline in each group. 1 woman needed ascites tapped, and the remaining 29 women received 6% HES infusion
Outcomes	Moderate and severe OHSS: classification not described but according to Golan and colleagues (Golan 1989) criteria (from private correspondence with author) • Severe OHSS (cabergoline group vs coasting group): 5/30 vs 4/30 • Moderate OHSS: not stated • Total OHSS: not stated Live birth rate: not stated Miscarriage rate (cabergoline group vs coasting group): 0/30 vs 2/30 Clinical pregnancy rate (defined as presence of gestational sac or cardiac activity 3 weeks after transfer) (cabergoline group vs coasting group): 8/30 vs 4/30 Multiple pregnancy rate (cabergoline group vs coasting group): 2/30 vs 0/30 Any other adverse effects of the treatment: cancelling of ET due to poor embryo quality (cabergoline group vs coasting group): 1/30 vs 1/30. Other adverse events not stated
Notes	Received draft of full-text article in peer review currently per private e-mail; additional information per private correspondence with first author.

Dalal 2014 *(Continued)*

	58 women received fluid of 6% HES and the remaining included woman received an ascites tap instead of HES.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Use of randomisation software (www.randomizer.org/).
Allocation concealment (selection bias)	Unclear risk	Independent research assistant allocated; concealment unclear.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding involved.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding involved.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts/loss of follow-up in the 2 groups.
Selective reporting (reporting bias)	Unclear risk	No exclusions (no live birth rate mentioned).
Other bias	High risk	29 participants in both groups also received HES infusion, 1 participant from each group had ascites tap, unclear which participant was involved.

Elnory 2018

Study characteristics

Methods	2-centre randomised controlled trial Computer-based randomisation Cabergoline vs calcium infusion Setting: Egypt
Participants	230 high-risk women undergoing IVF or ICSI, prior episodes of OHSS, polycystic ovaries (i.e. > 24 antral follicles present on baseline ultrasound), large number of small follicles (8–12 mm) seen on transvaginal ultrasound in earlier clinical observation, high serum E_2 at hCG trigger (E_2 > 3000 pg/mL or rapidly rising serum E_2) or > 20 retrieved oocytes Exclusion criteria: people with other endocrinopathies as hyperprolactinaemia, diabetes mellitus or congenital adrenal hyperplasia. Women with systemic diseases such as hypertension, bronchial asthma, or bleeding disorders Cabergoline group: 115 women Coasting group: 115 women
Interventions	Cabergoline group: cabergoline 0.5 mg/day for 7 days starting at day of ovum pick-up

Elnory 2018 *(Continued)*

	Calcium infusion group: 10 mL of calcium gluconate 10%, in 200 mL 0.9% saline solution IV on day of ovum pick-up and day 1, 2, and 3 after day of ovum pick-up over 30 minutes
Outcomes	Incidence of OHSS classified by Humaidan and colleagues (Humaidan 2010) • Severe OHSS (cabergoline vs calcium infusion): 4/115 vs 1/115 • Moderate OHSS (cabergoline vs calcium infusion): 10/115 vs 2/115 • Moderate or severe OHSS (cabergoline vs calcium infusion): 14/115 vs 3/115 Live birth rate (cabergoline vs calcium infusion): 48/115 vs 45/115 Miscarriage rate (early) (cabergoline vs calcium infusion): 10/115 vs 15/115 Clinical pregnancy rate (cabergoline vs calcium infusion): 58/115 vs 60/115 Multiple pregnancy rate: not stated Any other adverse effects of the treatment: not stated
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The trial statistician created a different sized blocked randomised treatment allocation schedule by using a computer random number generator.
Allocation concealment (selection bias)	Low risk	The treatment allocation schedule was stored by the infertility consultant, and the point of randomisation occurred when women were asked to enter, for ovum pick-up.
Blinding of participants and personnel (performance bias) All outcomes	High risk	After randomisation, blinding of either participants or staff who followed up participants was not possible due to nature of study.
Blinding of outcome assessment (detection bias) All outcomes	High risk	After randomisation, blinding of either participants or staff who followed up participants was not possible due to nature of study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	0 lost to follow-up.
Selective reporting (reporting bias)	Low risk	Most of outcomes were evaluated.
Other bias	Unclear risk	Only women with ICSI not IVF included, with only 16.5% and 17.9% male factor infertility… ICSI instead of IVF would affect pregnancy but not OHSS as an outcome.

El-Shaer 2019

Study characteristics

Methods	Randomised controlled study

El-Shaer 2019 *(Continued)*

	Cabergoline vs calcium gluconate infusion Setting: Egypt
Participants	170 women who were stimulated using the long luteal GnRHa protocol and at high risk for developing OHSS. Women with > 18 follicles (> 11 mm) and serum E_2 3000 pg/mL on day of HC administration were considered at risk for OHSS Between October 2016 and December 2018 No difference in age, BMI, basal FSH, antral follicle count, AMH level, cause, and duration of infertility Cabergoline group: 85 women Calcium gluconate infusion group: 85 women
Interventions	Cabergoline group: cabergoline 0.5 mg was administered once daily orally for 8 days starting on day of hCG administration Calcium gluconate infusion group: IV calcium gluconate (10%, 10 mL in 200 mL of physiological saline) was administered daily for 4 days starting on day of ovum pick-up
Outcomes	Moderate and severe OHSS: classification not described • Severe OHSS (cabergoline group vs calcium group): 1/85 vs 1/85 • Moderate OHSS (cabergoline group vs calcium group): 6/85 vs 8/85 • Total OHSS (cabergoline group vs calcium group): 7/85 vs 9/85 Live birth rate: not stated Miscarriage rate: not stated Clinical pregnancy rate (no definition) (cabergoline group vs calcium group): 30/85 vs 28/85 Multiple pregnancy rate: not stated Any other adverse effects of the treatment: no adverse events in either groups
Notes	ClinicalTrials.gov: NCT02875587 Dropouts not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Lack of sufficient information to permit judgement; randomisation in 1:1 ratio, but randomisation method unknown.
Allocation concealment (selection bias)	Unclear risk	Lack of sufficient information to permit judgement; only abstract available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Lack of sufficient information to permit judgement; only abstract available. probably unblinded as oral vs IV administration.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Lack of sufficient information to permit judgement.

El-Shaer 2019 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Life birth rate not reported in abstract.
Selective reporting (reporting bias)	Unclear risk	Dropouts or loss to follow-up not reported in abstract.
Other bias	Unclear risk	Lack of sufficient information to permit judgement; only abstract available.

Fetisova 2014

Study characteristics	
Methods	Randomised trial based on blinded envelopes Cabergoline vs no intervention Setting: Russia
Participants	168 women included, but only 128 high-risk women defined as transvaginal aspiration of ≥ 15 follicles Cabergoline group: 65 women Control group (no intervention): 63 women No significant difference between groups in somatic and obstetric anamnesis
Interventions	Cabergoline group: cabergoline 0.5 mg/day from the day after oocyte retrieval for 5 days before ET day Control group: no intervention
Outcomes	Moderate and severe OHSS, definition of OHSS not stated • Severe OHSS (cabergoline group vs control group): 3/65 vs 6/63 • Moderate OHSS (cabergoline group vs control group): 4/65 vs 13/63 • Total OHSS (cabergoline group vs control group): 7/65 vs 19/63 Live birth rate: not stated Miscarriage rate (cabergoline group vs control group): 4/65 vs 6/63 Clinical pregnancy rate (cabergoline group vs control group): 21/65 vs 23/63 Multiple pregnancy rate: not stated Any other adverse effects of the treatment: not stated
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Lack of information to permit judgement.
Allocation concealment (selection bias)	Low risk	Blinded envelopes method.

Fetisova 2014 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Lack of sufficient information to permit judgement.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Lack of sufficient information to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up.
Selective reporting (reporting bias)	Unclear risk	No exclusions (no live birth rate mentioned).
Other bias	Unclear risk	Lack of sufficient information to permit judgement.

Ghahiri 2015

Study characteristics	
Methods	Randomised controlled trial based on random number table Cabergoline vs albumin vs HES Setting: Iran
Participants	91 high-risk women with E_2 > 3000 pg/mL or > 20 follicles on day of hCG administration or previous history of OHSS, or a combination Cabergoline group: 31 women Albumin group: 30 women HES group: 30 women No significant difference between groups regarding gravidity, parity, death, ectopic pregnancy, abortion, and mean age
Interventions	Cabergoline group: cabergoline 0.5 mg daily for 7 days after oocyte retrieval Albumin group: 2 vials (2 × 50 mL) HAs IV 30 minutes after oocyte retrieval within 4 hours HES group: 1000 mL of 6% HES IV 30 minutes after oocyte retrieval within 4 hours
Outcomes	Moderate and severe OHSS identified by the classification of Golan and colleagues (Golan 1989) • Severe OHSS (cabergoline group vs albumin group vs HES group): 1/31 vs 3/30 vs 0/30 • Moderate OHSS (cabergoline group vs albumin group vs HES group): 4/31 vs 2/30 vs 2/30 • Total OHSS (cabergoline group vs albumin group vs HES group): 5/31 vs 5/30 vs 2/30 Live birth rate: not stated Miscarriage rate: not stated Clinical pregnancy rate: not stated Multiple pregnancy rate: not stated

Ghahiri 2015 *(Continued)*

	Any other adverse effects of the treatment: not stated
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table.
Allocation concealment (selection bias)	Unclear risk	Lack of sufficient information to permit judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Lack of sufficient information to permit judgement.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Lack of sufficient information to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up.
Selective reporting (reporting bias)	Unclear risk	No exclusions (no live birth rate mentioned).
Other bias	Unclear risk	Lack of sufficient information to permit judgement.

Jellad 2017

Study characteristics

Methods	Single-centre, prospective randomised study ("randomly divided in two groups") Cabergoline vs no medication Setting: Tunisia
Participants	146 women undergoing IVF or ICSI and receiving GnRHa. OHSS risk defined as a plasma E_2 > 3000 pg/mL on day of hCG administration or the development of ≥ 18 follicles > 12 mm in diameter, or both Exclusion criteria: coasting cases, aged > 40 years, history of uterine surgery, and submucosal and intramural fibromas > 5 cm Cabergoline group: 78 women Control group: 68 women
Interventions	Cabergoline group: cabergoline 0.5 mg/day for 8 days starting on day of hCG injection Control group (no intervention): no medication treatment
Outcomes	Moderate and severe OHSS identified according to the criteria of Golan and colleagues (Golan 1989)

Jellad 2017 *(Continued)*

- Severe OHSS (cabergoline group vs control group): 2/78 vs 8/68
- Moderate OHSS (cabergoline group vs control group): 8/78 vs 17/68
- Mild, moderate, or severe OHSS (cabergoline group vs control group): 25/78 vs 25/68

Live birth rate: not stated

Miscarriage rate: only reported for women who developed OHSS (cabergoline group vs control group): 3/25 vs 6/25

Clinical pregnancy rate only reported for women who developed OHSS (cabergoline group vs control group): 20/25 vs 14/25

Multiple pregnancy rate: not stated

Any other adverse effects of the treatment: not stated

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Lack of information to permit judgement.
Allocation concealment (selection bias)	Unclear risk	Lack of information to permit judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Lack of sufficient information to permit judgement.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Lack of sufficient information to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	High risk	No follow-up data from the non-OHSS women in both groups, no data on possible loss to follow-up or dropout.
Selective reporting (reporting bias)	High risk	Pregnancy data from the non-OHSS women in both groups not reported.
Other bias	Unclear risk	Coasting cases (women at highest risk for severe OHSS) were excluded, unclear based on what criteria coasting was opted for.

Kilic 2015

Study characteristics

Methods

Single-centre randomised controlled trial

Computer-based randomisation

Cabergoline vs no cabergoline

Kilic 2015 *(Continued)*

	Setting: Turkey
Participants	70 high-risk women undergoing IVF or ICSI, E_2 > 3000 pg/mL on day of hCG and with ≥ 20 follicles > 12 mm Exclusion criteria: E_2 ≥ 5000 pg/mL Cabergoline group: 36 women No cabergoline group: 34 women
Interventions	Cabergoline group: cabergoline 0.5 mg/day for 8 days from the day of hCG administration No cabergoline group: did not receive cabergoline
Outcomes	Incidence of OHSS classified by Golan and colleagues (Golan 1989) • Severe OHSS (cabergoline vs no cabergoline): 0/36 vs 5/34 • Moderate OHSS (cabergoline vs no cabergoline): 3/36 vs 2/34 • Moderate or severe OHSS (cabergoline vs no cabergoline): 3/36 vs 7/34 Live birth rate (cabergoline vs no cabergoline):8/36 vs 7/34 Miscarriage rate: not stated Clinical pregnancy rate (cabergoline vs no cabergoline): 6/36 vs 5/34 Multiple pregnancy rate: not stated Any other adverse effects of the treatment: not stated
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	On day of hCG administration, couples were allocated by a series of computer-generated random numbers into 2 groups.
Allocation concealment (selection bias)	Unclear risk	Lack of information to permit judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Lack of sufficient information to permit judgement.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Lack of sufficient information to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	Low risk	0 lost to follow-up.
Selective reporting (reporting bias)	Low risk	Most of outcomes were evaluated.
Other bias	Unclear risk	E_2 ≥ 5000 pg/mL were excluded, who are the women most at risk for OHSS.

Matorras 2013

Study characteristics	
Methods	Blinded randomised controlled trial Randomisation based on computer-generated numbers in sequentially numbered sealed envelopes Cabergoline + 6% HES vs 6% HES Setting: Spain
Participants	182 women undergoing IVF using their own oocytes and receiving GnRHa treatment and considered at risk of OHSS (all aged < 40 years). OHSS risk defined as a plasma E_2 > 3000 pg/mL on day of hCG administration or development of 20 follicles > 12 mm, or both Exclusion criteria: E_2 > 5000 pg/mL where cycles were cancelled Cabergoline group: 88 women Control group: 94 women
Interventions	Cabergoline group: slow IV infusion of 500 mL of 6% HES during follicle aspiration + cabergoline 0.5 mg orally for 8 days starting on day of hCG administration Control group: slow IV infusion of 500 mL of 6% HES during follicle aspiration
Outcomes	Moderate and severe OHSS identified by the modified classification of Golan and colleagues (Golan 1989) • Severe OHSS (cabergoline + HES group vs control group): 2/88 vs 1/94 • Moderate OHSS (cabergoline + HES group vs control group): 3/88 vs 2/94 • Total OHSS (cabergoline + HES group vs control group): 5/88 vs 3/94 Live birth rate: not stated Miscarriage rate (cabergoline + HES group vs control group): 5/88 vs 9/94 Clinical pregnancy rate (cabergoline + HES group vs control group): 43/88 vs 48/94 Multiple pregnancy rate: not stated Any other adverse effects of the treatment: not stated
Notes	ClinicalTrials.gov Identifier: NCT01530490

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation was performed using computer-generated numbers.
Allocation concealment (selection bias)	Low risk	Sequentially numbered sealed envelopes were used.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both the embryologists and the gynaecologists performing oocyte aspiration, ET, and post-transfer follow-up were blinded to the coadministration of cabergoline. Participants were not blinded; however, low risk of causing bias.

Matorras 2013 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Both the embryologists and the gynaecologists performing oocyte aspiration, ET, and post-transfer follow-up were blinded to the co-administration of cabergoline.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up.
Selective reporting (reporting bias)	Unclear risk	No exclusions (no live birth rate mentioned).
Other bias	Unclear risk	High-risk cycles were cancelled (E_2 > 5000 pg/mL), which might have excluded severe OHSS cases.

Saad 2017

Study characteristics	
Methods	Single-centre randomised controlled trial Cabergoline vs diosmin Setting: Egypt
Participants	200 high-risk women undergoing ICSI, previous episodes of OHSS, polycystic ovaries (i.e. > 24 antral follicles present on baseline ultrasound examination), high AMH (> 3.0 ng/mL), large number of small follicles (8–12 mm) seen on ultrasound during ovarian stimulation, high serum E_2 at hCG trigger (E_2 > 3000 pg/mL or rapidly rising serum E_2), presence of > 20 follicles by ultrasound on day of retrieval or large number of oocytes retrieved (> 20) Exclusion criteria: none Cabergoline group: 100 women Diosmin group: 100 women
Interventions	Cabergoline group: cabergoline 0.5 mg/day orally for 8 days starting at day of hCG injection Diosmin group: diosmin 1000 mg/8 hours orally for 2 weeks starting at the day of hCG injection
Outcomes	Incidence of OHSS classified by Golan and colleagues (Golan 1989) • Severe OHSS (cabergoline vs diosmin): 13/100 vs 2/100 • Moderate OHSS (cabergoline vs diosmin): 28/100 vs 12/100 Live birth rate: not stated Miscarriage rate (early) (cabergoline vs diosmin): 6/100 vs 5/100 Clinical pregnancy rate (cabergoline vs diosmin): 55/100 vs 58/100 Multiple pregnancy rate (cabergoline vs diosmin): 18/100 vs 21/100 Any other adverse effects of the treatment: not stated
Notes	
Risk of bias	

Saad 2017 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Lack of information to permit judgement.
Allocation concealment (selection bias)	Unclear risk	Lack of information to permit judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Lack of information to permit judgement.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Lack of information to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	Low risk	0 lost to follow-up.
Selective reporting (reporting bias)	Unclear risk	No live birth rate or adverse events mentioned.
Other bias	Unclear risk	Lack of information to permit judgement.

Salah 2012

Study characteristics	
Methods	Blinded randomised controlled trial Cabergoline vs prednisolone vs no intervention Setting: United Arab Emirates
Participants	200 women with polycystic ovarian syndrome undergoing IVF treatment and possibility of developing OHSS Exclusion criteria: previous oophorectomy, immune diseases that affect the permeability of blood vessels, such as systemic lupus, disseminated sclerosis, and rheumatoid arthritis Cabergoline group: 75 women, 2 women lost to follow-up Prednisolone group: 75 women, 3 women lost to follow-up Control group (no intervention): 50 women, 2 women lost to follow-up
Interventions	Cabergoline group: cabergoline 0.5 mg tablets, 1 tablet on 2 successive days, starting from day of hCG injection, and repeated 1 week later Prednisolone group: prednisolone 10 mg tablets twice a day to day of pregnancy test Control group: no intervention
Outcomes	Moderate and severe OHSS identified by the modified classification of Golan and colleagues (Golan 1989)

Salah 2012 *(Continued)*

	• Severe OHSS (cabergoline group vs control group): 0/75 vs 2/50 • Moderate OHSS (cabergoline group vs control group): 2/75 vs 4/50 • OHSS (cabergoline group vs prednisolone group vs control group): 2/75 vs 7/75 vs 6/50 Live birth rate: not stated Miscarriage rate: not stated Clinical pregnancy rate: not stated Multiple pregnancy rate: not stated Any other adverse effects of the treatment: not stated
Notes	No high-risk women identified (e.g. based on E_2 or ultrasound) except that this population was young women with PCOS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Lack of information to permit judgement.
Allocation concealment (selection bias)	Low risk	Sealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Lack of information to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	Low risk	7/200 women after randomisation could not complete their follow-up, no reasons stated.
Selective reporting (reporting bias)	Unclear risk	No exclusions (no live birth rates mentioned).
Other bias	High risk	No high-risk women identified (e.g. based on E_2 or ultrasound) except this population was young women with PCOS.

Shaltout 2012

Study characteristics

Methods	Randomised controlled trial Computer-based randomisation Cabergoline vs no intervention Setting: Egypt

Shaltout 2012 *(Continued)*

Participants	200 women undergoing ICSI treatment and at risk of developing OHSS, defined by E_2 > 3500 pg/mL on day of hCG with ≥ 20 follicles > 12 mm diameter Cabergoline group: 100 women; 2 had empty follicles, 2 had failure of fertilisation, and 1 discontinued Control group: 100 women; 3 had empty follicles and 1 had failure of fertilisation Exclusion criterion: E_2 ≥ 5000 pg/mL No differences between the groups in age, BMI, and causes of infertility
Interventions	Cabergoline group: cabergoline tablet 0.25 mg/day for 8 days from the day of hCG injection Control group: no intervention
Outcomes	Moderate and severe OHSS identified according to Golan and colleagues (Golan 1989) • Severe OHSS (cabergoline group vs control group): 1/100 vs 3/100 • Moderate OHSS (cabergoline group vs control group): 4/100 vs 11/100 Live birth rate (cabergoline group vs control group): 37/100 vs 36/100 Miscarriage rate (cabergoline group vs control group): 5/100 vs 5/100 Clinical pregnancy rate (cabergoline group vs control group): 42/100 vs 41/100 Multiple pregnancy rate: not stated Any other adverse effects of the treatment: not stated
Notes	Number of women excluded for dropout (no ET because no oocytes found, no embryos yielded, etc., 1 adverse event)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-based randomisation method.
Allocation concealment (selection bias)	Unclear risk	Lack of sufficient information to permit judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Lack of sufficient information to permit judgement.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Lack of information to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	Low risk	9 women could not complete their follow-up but exact reasons not stated.
Selective reporting (reporting bias)	Low risk	Most outcomes were included.
Other bias	Unclear risk	Lack of sufficient information to permit judgement.

Singh 2017

Study characteristics	
Methods	Single-centre randomised controlled trial Computer-based randomisation Cabergoline vs placebo Setting: India
Participants	110 high-risk women undergoing IVF/ICSI with ≥ 13 follicles ≥ 11 mm on day of hCG trigger Exclusion criteria: women who would have < 15 oocytes retrieved Cabergoline group: 55 women, 3 did not receive allocated intervention Placebo group: 55 women, 2 lost to follow-up and 3 discontinued intervention
Interventions	Cabergoline group: cabergoline Placebo group: placebo
Outcomes	Incidence of OHSS defined by Mathur's classification (Mathur 2007) • Severe OHSS (cabergoline vs placebo): 1/55 vs 1/55 • Moderate OHSS (cabergoline vs placebo): 9/55 vs 8/55 Live birth rate (cabergoline vs placebo): 10/55 vs 12/55 Miscarriage rate: not stated Clinical pregnancy rate (cabergoline vs placebo): 14/55 vs 16/55 Multiple pregnancy rate not stated Any other adverse effects of the treatment: not stated
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Using the computer-generated model by an independent doctor who was not involved in the study.
Allocation concealment (selection bias)	Unclear risk	Lack of information to permit judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Lack of sufficient information to permit judgement.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Lack of information to permit judgement.

Singh 2017 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	3 women from the cabergoline group were withdrawn due to an intolerance of medication due to nausea and headache. From the placebo group, 5 women were excluded from the study; of these, 2 women missed a follow-up visit and 3 women had an E_2 > 6000 pg/mL on day of trigger. Those women would probably develop moderate or severe OHSS.
Selective reporting (reporting bias)	Low risk	Most outcomes were evaluated.
Other bias	Unclear risk	Lack of sufficient information to permit judgement.

Sohrabvand 2009

Study characteristics	
Methods	Parallel design, randomised controlled trial Block randomisation Cabergoline vs coasting Setting: Iran
Participants	60 women at risk of OHSS defined by ≥ 20 follicles in both ovaries, most being ≤ 14 mm in diameter and serum E_2 3000 pg/mL Cabergoline group: 30 women Coasting group: 30 women Exclusion criterion: contraindication to dopamine agonists No significant differences between groups in age, BMI, menstrual cycle pattern, duration of infertility, and causes of infertility
Interventions	Cabergoline group: cabergoline tablet 0.5 mg/day for 7 days after hCG administration Coasting group: gonadotropin administration was ceased until serum E_2 < 3000 pg/mL before hCG administration
Outcomes	Moderate and severe OHSS identified by the classification of Golan and colleagues (Golan 1989) • Severe OHSS (cabergoline group vs coasting group): 0/30 vs 0/30 • Moderate OHSS (cabergoline group vs coasting group): 1/30 vs 7/30 • Total OHSS (cabergoline group vs coasting group): 1/30 vs 7/30 Live birth rate: not stated Miscarriage rate: not stated Clinical pregnancy rate (cabergoline group vs coasting group): 14/30 vs 7/30 Multiple pregnancy rate: not stated Any other adverse effects of the treatment: not stated
Notes	

Sohrabvand 2009 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table blocks according to Biostatistics in Health Systems.
Allocation concealment (selection bias)	Unclear risk	Lack of sufficient information to permit judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Lack of sufficient information to permit judgement.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Lack of information to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up.
Selective reporting (reporting bias)	Unclear risk	No exclusions (no live birth rate mentioned).
Other bias	Unclear risk	Lack of sufficient information to permit judgement.

Tehraninejad 2012

Study characteristics	
Methods	Parallel, single-centre randomised controlled trial Not blinded Computer-based randomisation Cabergoline vs HA Setting: Iran
Participants	140 women aged 15–37 years Inclusion criteria: risk of developing OHSS, defined by the development of 20–30 follicles > 12 mm in diameter on day of hCG administration and retrieval of > 20 oocytes, ovarian stimulation with long protocol Exclusion criteria: coasting cases, aged > 37 years, previous uterine surgery, intramural or submucosal myoma sizes > 5 cm Cabergoline group: 70 women, 1 woman lost to follow-up Albumin group: 70 women, 1 woman lost to follow-up No differences between groups in age, BMI, duration of infertility, type of infertility, basal FSH, LH levels, and E_2 levels on day of hCG administration but there was a difference in cause of infertility.

Tehraninejad 2012 *(Continued)*

Interventions	Cabergoline group: cabergoline tablet 0.5 mg/day 7 days beginning on day of oocyte retrieval Control group: HA 20% IV infusion
Outcomes	Moderate and severe OHSS identified by the modified classification of Golan and colleagues (Golan 1989) • Severe OHSS (cabergoline group vs control group): 1/70 vs 16/70 • Moderate OHSS (cabergoline group vs control group): 14/70 vs 33/70 Live birth rate: not stated Miscarriage rate (cabergoline group vs control group): 1/70 vs 3/70 Clinical pregnancy rate (cabergoline group vs control group): 20/70 vs 26/70 Multiple pregnancy rate (cabergoline group vs control group): 3/70 vs 5/70 Any other adverse effects of the treatment: not stated
Notes	1 dropout in each group. Not reported when they dropped out or if they had even started. Excluded from analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-based randomisation method.
Allocation concealment (selection bias)	Unclear risk	Lack of sufficient information to permit judgement.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: "Our study was not blinded because we have ethical limitations for using placebo for high risk patients."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Lack of information to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	Low risk	2/140 women lost to follow-up.
Selective reporting (reporting bias)	Unclear risk	No exclusions (no live birth rate mentioned).
Other bias	Unclear risk	Lack of sufficient information to permit judgement.

Torabizadeh 2013

Study characteristics

Methods	Single-centre, randomised controlled trial Blinded for sampling. No statement on blinding for allocation

Torabizadeh 2013 *(Continued)*

	Randomisation not described Cabergoline vs HA Setting: Iran
Participants	95 women, every other participant sampled. > 20 oocytes during oocyte retrieval, ovary size > 10 cm, serum E_2 > 2500 pg/mL, considered eligible if high risk with > 20 follicles; randomisation when confirmed > 20 follicles retrieved in both ovaries at day of hCG injection Exclusion criterion: < 20 oocytes retrieved Cabergoline group: 47 women Albumin group: 48 women
Interventions	Cabergoline group: cabergoline 0.5 mg/day orally from day of hCG injection to 8 days Control group: 10 units IV HA at the start of oocyte retrieval
Outcomes	Moderate and severe OHSS; identified/classification not described other than "classified according to related criteria" • Severe OHSS (cabergoline group vs control group): 1/47 vs 5/48 • Moderate OHSS (cabergoline group vs control group): 3/47 vs 5/48 Live birth rate: not stated Miscarriage rate: not stated Clinical pregnancy rate: not stated Multiple pregnancy rate: not stated Any other adverse effects of the treatment: not stated
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "The method of sampling was randomized sampling as we selected every other person. Randomization was used to allocate the patients to two groups immediately after confirmation of retrieval of >20 oocytes. but intervention started already on day 2 before retrieval (hCG administration)."
Allocation concealment (selection bias)	Unclear risk	Lack of sufficient information to permit judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Lack of sufficient information to permit judgement.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Lack of information to permit judgement.
Incomplete outcome data (attrition bias)	Low risk	No loss to follow-up.

Torabizadeh 2013 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Unclear risk	No exclusions (no live birth rate mentioned).
Other bias	Unclear risk	Lack of sufficient information to permit judgement.

AMH: anti-Müllerian hormone; BMI: body mass index; E_2: oestradiol; ET: embryo transfer; FSH: follicle-stimulating hormone; GnRH: gonadotropin-releasing hormone; GnRHa: gonadotropin-releasing hormone agonist; HA: human albumin; hCG: human chorionic gonadotrophin; HES: hydroxyethyl starch; hMG: human menopausal gonadotrophin; ICSI: intracytoplasmic sperm injection; IV: intravenous; IVF: in vitro fertilisation; LH: luteinising hormone; OHSS: ovarian hyperstimulation syndrome; PGD: preimplantation genetic diagnosis; VEGF: vascular endothelial growth factor; WHO: World Health Organization.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Aflatoonian 2008	Not randomised. Quote: "divided into two groups according to patients convenience."
Agha Hosseini 2010	Not an RCT; historic control group.
Alvarez 2007b	A pilot study, not an RCT.
Ata 2009	Case report.
Fouda 2016	Studied co-intervention plus cabergoline rather than cabergoline.
Ghaebi 2016	Only women who had already developed signs of (mild) OHSS included.
Gualtieri 2011	Retrospective analysis, not an RCT.
Guvendag 2010	Case control study, not an RCT.
Hatton 2012	Retrospective study, not an RCT.
Hosseini 2011	Not an RCT.
Khan 2010	Not an RCT.
Naredi 2013	Quasi-randomised, odd/even participants appointed to intervention groups.
Rollene 2009a	Case series.
Rollene 2009b	Retrospective cohort study.
Saad 2016	Quasi-randomised (odd and even numbers).
Saad 2019	Diosmin + cabergoline vs cabergoline.
Seow 2013	2 differently timed cabergoline regimens, no control group.
Seyam 2018	Laparoscopic ovarian drilling vs GnRH antagonist combined with cabergoline.

Study	Reason for exclusion
Sherwal 2010	Historical matched control group.
Soliman 2011	Not an RCT.
Spitzer 2011	Retrospective study.
Zahran 2018	No ART.
Zargar 2011	Evaluated 2 different cabergoline regimens on prevention of OHSS.

ART: assisted reproduction technology; GnRH: gonadotropin-releasing hormone; OHSS: ovarian hyperstimulation syndrome; RCT: randomised controlled trial.

Characteristics of studies awaiting classification *[ordered by study ID]*

Ahmadi 2010

Methods	Prospective randomised controlled trial Cabergoline vs human albumin
Participants	112 high-risk women undergoing ART Cabergoline group: 56 women Albumin group: 56 women No statistically significant differences in age, BMI, number of follicles and oocyte retrieved, and serum E_2 on day of hCG injection
Interventions	Cabergoline group: cabergoline tablet 0.5 mg/day until 12 days from oocytes retrieval Albumin group: 20 g IV human albumin on day of oocyte retrieval
Outcomes	The OHSS frequency was significantly lower in the cabergoline group ($P < 0.001$). There were no significant differences in pregnancy rate, implantation, and miscarriages between groups.
Notes	Meeting abstract, no results mentioned, no response from authors yet.

ART: assisted reproduction technology; BMI: body mass index; E_2: oestradiol; hCG: human chorionic gonadotrophin; IV: intravenous; OHSS: ovarian hyperstimulation syndrome.

Characteristics of ongoing studies *[ordered by study ID]*

El Khattan 2015

Study name	Comparative study between cabergoline and intravenous calcium in the prevention of ovarian hyperstimulation in women with polycystic ovarian disease undergoing intracytoplasmic sperm injection (ICSI)
Methods	
Participants	
Interventions	Cabergoline group: cabergoline (Dostinex) 0.5 mg/day oral tablets for 8 days from the day of hCG injection

El Khattan 2015 *(Continued)*

	Calcium gluconate group: intravenous infusion of 10% calcium gluconate 10 mL in 200 mL of physiological saline on day of ovum pick-up Once in the treatment cycle and each participant will undergo 1 treatment cycle during the trial To monitor adherence to medication, participant will return surplus tablets
Outcomes	Primary outcomes: • occurrence of OHSS – diagnosed clinically by participant's monitoring symptoms accompanied by ultrasonography and laboratory investigation • severity of OHSS – detected by need for ascitic drainage and need for hospitalisation Secondary outcomes: • chemical pregnancy rate: positive (serum β-hCG) 14 days following ET • clinical pregnancy rate: positive pregnancy test and fetal heartbeat by ultrasound after 6 weeks' gestational age • miscarriage rate: diagnosed by ultrasound/clinically • ectopic rate: diagnosed by ultrasound/clinically
Starting date	July 2013
Contact information	emyelkattan@gmail.com
Notes	

Hendricks 2015

Study name	Study of cabergoline for prevention of ovarian hyperstimulation syndrome (OHSS) in in vitro fertilization cycles and derivation of OHSS biomarkers
Methods	Randomised controlled trial Endpoint classification: efficacy study Intervention model: parallel assignment Masking: double blind (participant, carer, investigator, outcomes assessor) Primary purpose: prevention
Participants	Inclusion criterion: • women with > 20 oocytes collected after controlled ovarian hyperstimulation in both GnRH agonist and antagonist cycles Exclusion criteria: • allergy to dopamine agonists • undergoing in vitro maturation cycles • where GnRH analogues have been used to trigger oocyte maturation in antagonist cycles
Interventions	Cabergoline group: cabergoline 0.5 mg tablet daily for 8 days Control group: placebo 1 tablet daily for 8 days
Outcomes	Primary outcome:

Hendricks 2015 *(Continued)*

- development of moderate or severe OHSS necessitating admission for management of OHSS (time frame: within 2 weeks after hCG trigger) (designated as safety issue: no)

Secondary outcome:

- need for abdominal or pleural tap (time frame: within 3 weeks after hCG trigger) (designated as safety issue: no)
- other complications of OHSS (venous thromboembolism, cardiac failure, renal failure, acute respiratory failure, pulmonary oedema, and coma) (time frame: within 3 weeks after hCG trigger) (designated as safety issue: no)
- admission into intensive care unit (time frame: within 3 weeks after hCG trigger) (designated as safety issue: no)
- examination of potential biomarkers for OHSS (time frame: 1 to 2 years) (designated as safety issue: no)

Starting date	15 February 2012
Contact information	mariannehendricksemail@gmail.com
Notes	NCT01535859

IRCT2016071428930N1

Study name	Effects of calcium in the prevention of ovarian hyperstimulation syndrome in patients undergoing IVF/ICSI
Methods	Randomised single blinded trial
Participants	Women at high risk of ovarian hyperstimulation; PCO; women with > 20 follicles > 12 mm during oocyte retrieval; history of OHSS in previous cycles; E_2 > 2500 pg/mL on day of hCG administration Exclusion criteria: diabetes; hypertension; asthma; blood pressure, and heart disease
Interventions	Cabergoline + calcium group (93 women): cabergoline 5 mg/day twice a day at day of hCG injection to 5 days + intravenous infusion of 10 mL 10% calcium gluconate in 200 mL 0.9% saline solution on day of ovum pick-up and days 1, 2, and 3 Cabergoline group (93 women): cabergoline 5 mg/day twice a day at day of hCG injection to 5 days
Outcomes	Dosage of hMG used, total number of follicles developed, number of oocytes retrieved, serum E_2 concentrations during the luteal phase, development of ascites, number of embryos generated clinical pregnancy rate, results of the IVF-ET cycles, and incidence and severity of any OHSS
Starting date	1 April 2016
Contact information	Maliha Mahmoudinia (mahmoudiniam941@mums.ac.ir)
Notes	

Kamel 2015

Study name	Effect of cabergoline on endometrial vascularity during intracytoplasmic sperm injection
Methods	Allocation: non-randomised

Kamel 2015 *(Continued)*

	Endpoint classification: efficacy study Intervention model: parallel assignment Masking: open label Primary purpose: diagnostic
Participants	Inclusion criteria: aged 18–40 years; normal serum prolactin level; tubal factor infertility; unexplained infertility; BMI ≥ 30 kg/m^2; E_2 > 3500 pg/mL on day of ovulation trigger; underwent coasting for OHSS prevention; > 20 follicles ≥ 11 mm on day of final oocyte maturation Exclusion criteria: contraindication to pregnancy, e.g. somatic and mental diseases that are contraindications for carrying of a pregnancy and childbirth, inborn malformations or acquired deformations of uterus cavity that make embryo implantation or carrying of a pregnancy impossible, or ovarian tumours; severe male factor infertility; women with hyperprolactinaemia; frozen ET cycles; uterine anomalies; uterine synechia; history of genital tuberculosis; repeated implantation failure in ICSI; taking medication that is known to alter prolactin levels, e.g. antipsychotics, atypical agents, and risperidone; thyroid dysfunction; medical disorders affecting serum prolactin, e.g. acromegaly, chronic renal failure, and hypothyroidism
Interventions	Cabergoline group: women AT RISK of OHSS receiving cabergoline 0.5 mg/day for 8 days from the day of oocyte pick-up for prevention of hyperstimulation Control group: women AT RISK of OHSS not receiving cabergoline Control group 2: will serve as a control group and will include age- and BMI-matched women NOT AT RISK of OHSS, and not receiving cabergoline
Outcomes	Primary outcome: • pregnancy rate (chemical, clinical) (time frame: 2 weeks after ET) (designated as safety issue: no). β-hCG) > 10 IU on day 12 after ET Secondary outcomes: • miscarriage rate (time frame: 3 weeks after positive β-hCG) (designated as safety issue: no). First ultrasound at 7 weeks' gestation • OHSS rate (time frame: 4 weeks) (designated as safety issue: no). Early- and late-onset OHSS • vascularisation index (time frame: 5 days) (designated as safety issue: no). 3D ultrasound and power Doppler examination done before ovum pick-up and repeated before transfer • flow index (time frame: 5 days) (designated as safety issue: no). 3D ultrasound and power Doppler examination done before ovum pick-up and repeated before transfer • vascularisation flow index (time frame: 5 days) (designated as safety issue: no). 3D ultrasound and power Doppler examination done before ovum pick-up and repeated before transfer • pulsatility index (time frame: 5 days) (designated as safety issue: no). 3D ultrasound and power Doppler examination done before ovum pick-up and repeated before transfer • resistance index (time frame: 5 days) (designated as safety issue: no). 3D ultrasound and power Doppler examination done before ovum pick-up and repeated before transfer • peak systolic velocity (time frame: 5 days) (designated as safety issue: no). 3D ultrasound and power Doppler examination done before ovum pick-up and repeated before transfer • end-diastolic velocity (time frame: 5 days) (designated as safety issue: no). 3D ultrasound and power Doppler examination done before ovum pick-up and repeated before transfer
Starting date	December 2014
Contact information	Dr.ahmed.m.kamel@gmail.com
Notes	NCT02306564

Khaled 2014

Study name	Diosmin versus cabergoline for prevention of ovarian hyperstimulation syndrome (infertility)
Methods	Allocation: randomised Endpoint classification: safety/efficacy study Intervention model: single group assignment Masking: single blind (participant) Primary purpose: prevention
Participants	200 women at risk of OHSS during ICSI cycles will be randomly scheduled into 2 equal groups Inclusion criteria: infertile women undergoing ICSI or polycystic ovarian syndrome, aged 23–48 years with 1 of the following: • presence of > 20 follicles by ultrasound • E_2 > 3000 pg/mL • retrieval of > 15 follicles Exclusion criteria: none
Interventions	Diosmin group: diosmin 2 × 500 mg tablets every 8 hours will be given from day of hCG injection for 14 days Cabergoline group: cabergoline 1 × 0.5 mg tablet/day will be given from day of hCG injection for 8 days
Outcomes	Primary outcome: • number of participants with OHSS (time frame: every 2 weeks for 8 weeks) (designated as safety issue: yes). Assessed by: abdominal bloating, mild abdominal pain, nausea and vomiting, oliguria, acute respiratory distress syndrome, ultrasound (ovarian size usually > 8 cm), ultrasound evidence of ascites, laboratory haemoconcentration, haematocrit > 45%, hypoproteinaemia Secondary outcomes: • pregnancy rate (time frame: 14 days after ET) (designated as safety issue: yes) • β-hCG (serum hCG test) will be checked 14 days after ET
Starting date	May 2014
Contact information	dr.khalidkhader77@yahoo.com
Notes	NCT02134249

3D: three dimensional; BMI: body mass index; E_2: oestradiol; ET: embryo transfer; GnRH: gonadotropin-releasing hormone; hCG: human chorionic gonadotrophin; hMG: human menopausal gonadotrophin; ICSI: intracytoplasmic sperm injection; IVF: in vitro fertilisation; OHSS: ovarian hyperstimulation syndrome; PCO: polycystic ovary.

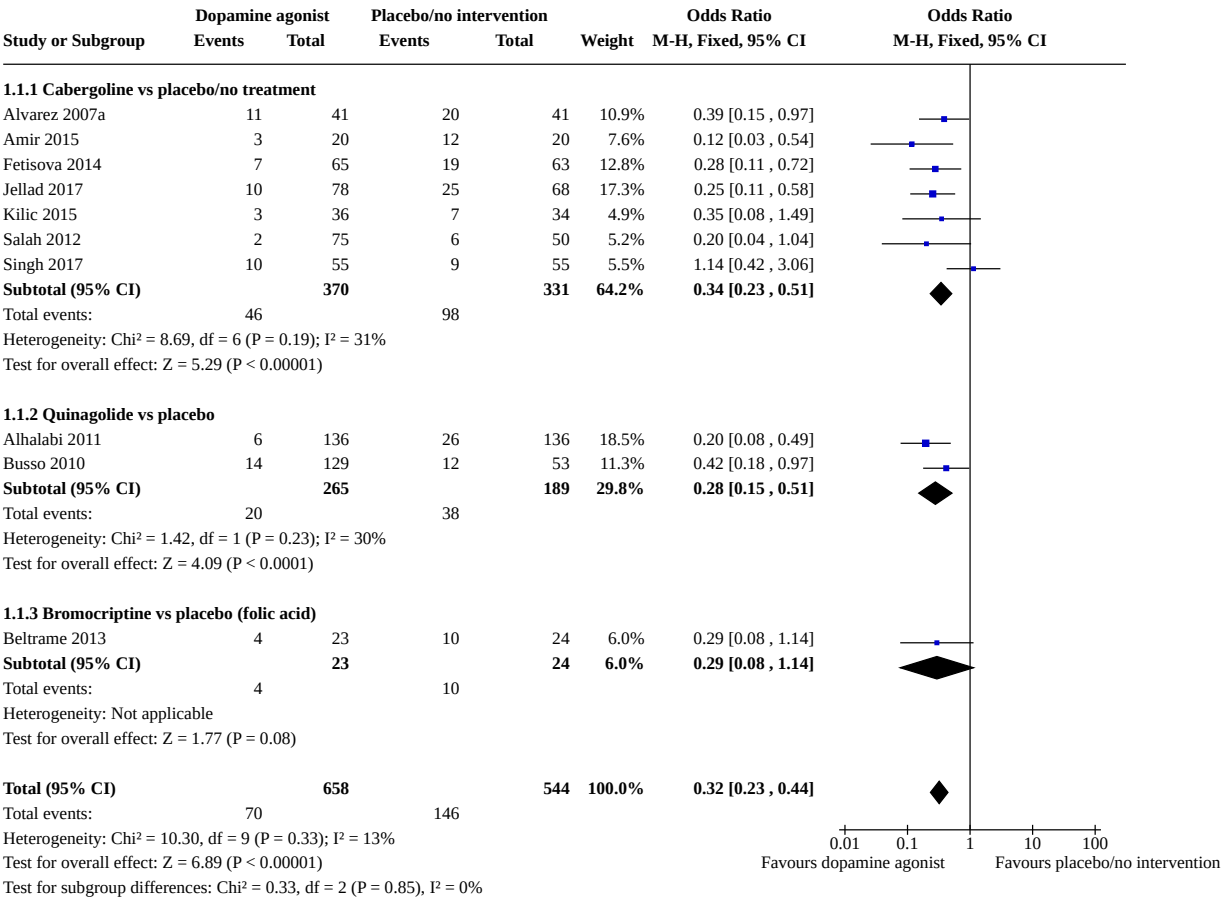
DATA AND ANALYSES

Comparison 1. Dopamine agonist versus placebo/no intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Incidence of moderate or severe ovarian hyperstimulation syndrome (OHSS)	10	1202	Odds Ratio (M-H, Fixed, 95% CI)	0.32 [0.23, 0.44]
1.1.1 Cabergoline vs placebo/no treatment	7	701	Odds Ratio (M-H, Fixed, 95% CI)	0.34 [0.23, 0.51]
1.1.2 Quinagolide vs placebo	2	454	Odds Ratio (M-H, Fixed, 95% CI)	0.28 [0.15, 0.51]
1.1.3 Bromocriptine vs placebo (folic acid)	1	47	Odds Ratio (M-H, Fixed, 95% CI)	0.29 [0.08, 1.14]
1.2 Subgroup analysis by severity of OHSS	9		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.2.1 Severe OHSS	9	930	Odds Ratio (M-H, Fixed, 95% CI)	0.27 [0.14, 0.51]
1.2.2 Moderate OHSS	9	930	Odds Ratio (M-H, Fixed, 95% CI)	0.46 [0.31, 0.68]
1.3 Live birth rate	3	362	Odds Ratio (M-H, Fixed, 95% CI)	0.96 [0.60, 1.55]
1.3.1 Cabergoline vs placebo/no treatment	2	180	Odds Ratio (M-H, Fixed, 95% CI)	0.91 [0.44, 1.87]
1.3.2 Quinagolide vs placebo/no treatment	1	182	Odds Ratio (M-H, Fixed, 95% CI)	1.01 [0.53, 1.91]
1.4 Clinical pregnancy rate	5	530	Odds Ratio (M-H, Fixed, 95% CI)	0.92 [0.63, 1.37]
1.4.1 Cabergoline vs placebo/no intervention	4	348	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.61, 1.64]
1.4.2 Quinagolide vs placebo/no treatment	1	182	Odds Ratio (M-H, Fixed, 95% CI)	0.81 [0.43, 1.54]
1.5 Multiple pregnancy rate	1	40	Odds Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 8.26]
1.5.1 Cabergoline vs placebo/no treatment	1	40	Odds Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 8.26]
1.6 Miscarriage rate	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.6.1 Cabergoline vs placebo/no treatment	2	168	Odds Ratio (M-H, Fixed, 95% CI)	0.66 [0.19, 2.28]
1.7 Any other adverse events	2	264	Odds Ratio (M-H, Fixed, 95% CI)	4.54 [1.49, 13.84]

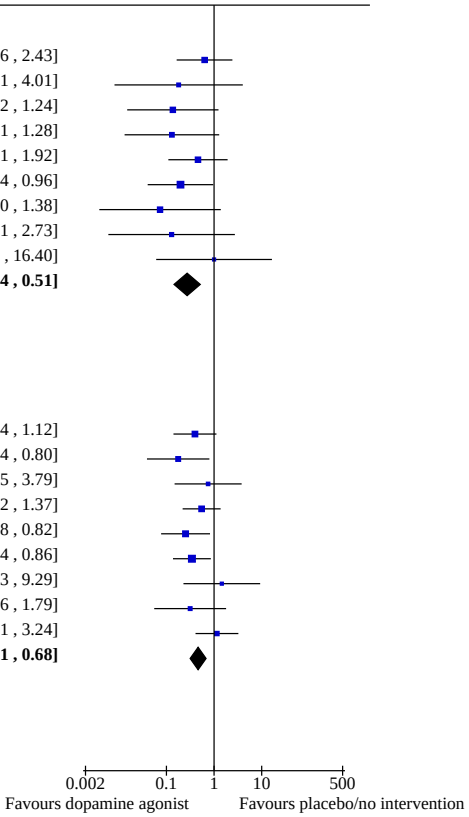
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.7.1 Cabergoline vs placebo/no treatment	1	82	Odds Ratio (M-H, Fixed, 95% CI)	2.24 [0.62, 8.14]
1.7.2 Quinagolide vs placebo	1	182	Odds Ratio (M-H, Fixed, 95% CI)	16.64 [0.98, 282.02]

Analysis 1.1. Comparison 1: Dopamine agonist versus placebo/no intervention, Outcome 1: Incidence of moderate or severe ovarian hyperstimulation syndrome (OHSS)



Analysis 1.2. Comparison 1: Dopamine agonist versus placebo/ no intervention, Outcome 2: Subgroup analysis by severity of OHSS

Study or Subgroup	Dopamine agonist Events	Total	Placebo/no intervention Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.2.1 Severe OHSS						
Alvarez 2007a	4	41	6	41	13.1%	0.63 [0.16 , 2.43]
Amir 2015 (1)	0	20	2	20	5.9%	0.18 [0.01 , 4.01]
Beltrame 2013	1	23	6	24	13.6%	0.14 [0.02 , 1.24]
Busso 2010	1	129	3	53	10.2%	0.13 [0.01 , 1.28]
Fetisova 2014	3	65	6	63	14.1%	0.46 [0.11 , 1.92]
Jellad 2017	2	78	8	68	20.1%	0.20 [0.04 , 0.96]
Kilic 2015	0	36	5	34	13.5%	0.07 [0.00 , 1.38]
Salah 2012	0	75	2	50	7.2%	0.13 [0.01 , 2.73]
Singh 2017	1	55	1	55	2.4%	1.00 [0.06 , 16.40]
Subtotal (95% CI)		**522**		**408**	**100.0%**	**0.27 [0.14 , 0.51]**
Total events:	12		39			
Heterogeneity: Chi² = 4.84, df = 8 (P = 0.77); I² = 0%						
Test for overall effect: Z = 4.03 (P < 0.0001)						
1.2.2 Moderate OHSS						
Alvarez 2007a	7	41	14	41	15.1%	0.40 [0.14 , 1.12]
Amir 2015	3	20	10	20	11.0%	0.18 [0.04 , 0.80]
Beltrame 2013	3	23	4	24	4.4%	0.75 [0.15 , 3.79]
Busso 2010	13	129	9	53	14.9%	0.55 [0.22 , 1.37]
Fetisova 2014	4	65	13	63	16.1%	0.25 [0.08 , 0.82]
Jellad 2017	8	78	17	68	21.2%	0.34 [0.14 , 0.86]
Kilic 2015	3	36	2	34	2.5%	1.45 [0.23 , 9.29]
Salah 2012	2	75	4	50	6.1%	0.32 [0.06 , 1.79]
Singh 2017	9	55	8	55	8.7%	1.15 [0.41 , 3.24]
Subtotal (95% CI)		**522**		**408**	**100.0%**	**0.46 [0.31 , 0.68]**
Total events:	52		81			
Heterogeneity: Chi² = 8.17, df = 8 (P = 0.42); I² = 2%						
Test for overall effect: Z = 3.93 (P < 0.0001)						
Test for subgroup differences: Chi² = 1.96, df = 1 (P = 0.16), I² = 49.1%						

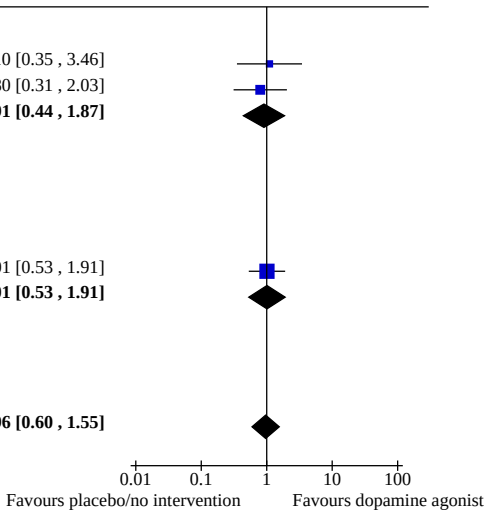


Footnotes

(1) This study also used coasting in both groups if applied if E_2 > 5000 pg/mL, but it was unclear to which participants this was applied

Analysis 1.3. Comparison 1: Dopamine agonist versus placebo/no intervention, Outcome 3: Live birth rate

Study or Subgroup	Dopamine agonist Events	Total	Placebo/no intervention Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.3.1 Cabergoline vs placebo/no treatment						
Kilic 2015	8	36	7	34	16.4%	1.10 [0.35 , 3.46]
Singh 2017	10	55	12	55	28.8%	0.80 [0.31 , 2.03]
Subtotal (95% CI)		**91**		**89**	**45.2%**	**0.91 [0.44 , 1.87]**
Total events:	18		19			
Heterogeneity: Chi² = 0.19, df = 1 (P = 0.67); I² = 0%						
Test for overall effect: Z = 0.26 (P = 0.79)						
1.3.2 Quinagolide vs placebo/no treatment						
Busso 2010 (1)	66	129	27	53	54.8%	1.01 [0.53 , 1.91]
Subtotal (95% CI)		**129**		**53**	**54.8%**	**1.01 [0.53 , 1.91]**
Total events:	66		27			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.03 (P = 0.98)						
Total (95% CI)		**220**		**142**	**100.0%**	**0.96 [0.60 , 1.55]**
Total events:	84		46			
Heterogeneity: Chi² = 0.23, df = 2 (P = 0.89); I² = 0%						
Test for overall effect: Z = 0.15 (P = 0.88)						
Test for subgroup differences: Chi² = 0.05, df = 1 (P = 0.83), I² = 0%						

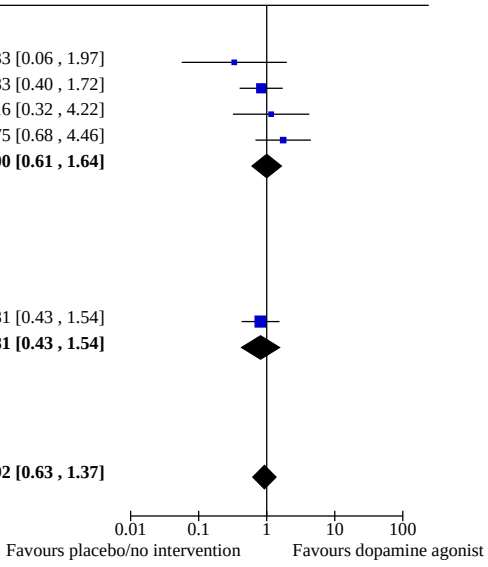


Footnotes

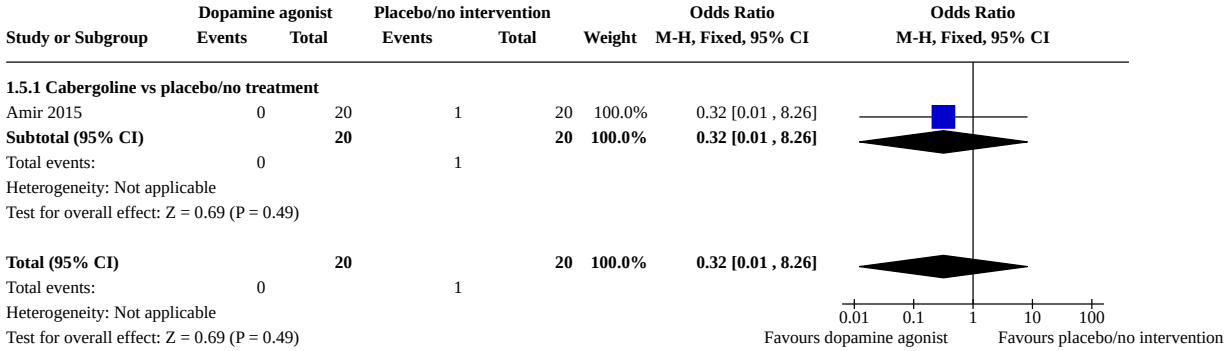
(1) For all dose groups in total.

Analysis 1.4. Comparison 1: Dopamine agonist versus placebo/no intervention, Outcome 4: Clinical pregnancy rate

Study or Subgroup	Dopamine agonist Events	Total	Placebo/no intervention Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.4.1 Cabergoline vs placebo/no intervention						
Amir 2015	2	20	5	20	8.6%	0.33 [0.06 , 1.97]
Fetisova 2014	21	65	23	63	30.4%	0.83 [0.40 , 1.72]
Kilic 2015	6	36	5	34	8.2%	1.16 [0.32 , 4.22]
Singh 2017	14	55	9	55	12.9%	1.75 [0.68 , 4.46]
Subtotal (95% CI)		**176**		**172**	**60.1%**	**1.00 [0.61 , 1.64]**
Total events:	43		42			
Heterogeneity: Chi² = 3.12, df = 3 (P = 0.37); I² = 4%						
Test for overall effect: Z = 0.00 (P = 1.00)						
1.4.2 Quinagolide vs placebo/no treatment						
Busso 2010	59	129	27	53	39.9%	0.81 [0.43 , 1.54]
Subtotal (95% CI)		**129**		**53**	**39.9%**	**0.81 [0.43 , 1.54]**
Total events:	59		27			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.64 (P = 0.52)						
Total (95% CI)		**305**		**225**	**100.0%**	**0.92 [0.63 , 1.37]**
Total events:	102		69			
Heterogeneity: Chi² = 3.39, df = 4 (P = 0.49); I² = 0%						
Test for overall effect: Z = 0.39 (P = 0.70)						
Test for subgroup differences: Chi² = 0.26, df = 1 (P = 0.61), I² = 0%						

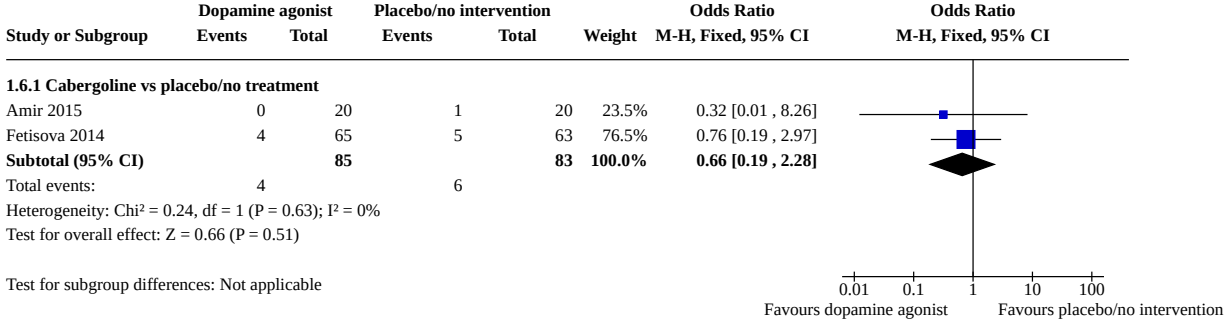


Analysis 1.5. Comparison 1: Dopamine agonist versus placebo/no intervention, Outcome 5: Multiple pregnancy rate



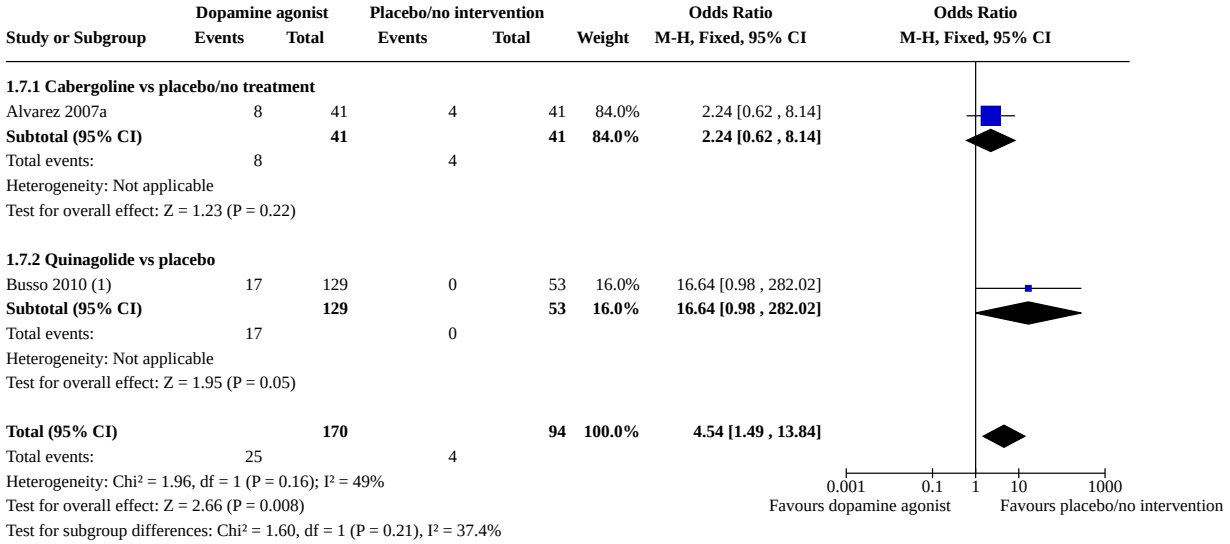
Study or Subgroup	Dopamine agonist Events	Total	Placebo/no intervention Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.5.1 Cabergoline vs placebo/no treatment						
Amir 2015	0	20	1	20	100.0%	0.32 [0.01 , 8.26]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**0.32 [0.01 , 8.26]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
Total (95% CI)		**20**		**20**	**100.0%**	**0.32 [0.01 , 8.26]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
Test for subgroup differences: Not applicable						

Analysis 1.6. Comparison 1: Dopamine agonist versus placebo/no intervention, Outcome 6: Miscarriage rate



Study or Subgroup	Dopamine agonist Events	Total	Placebo/no intervention Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.6.1 Cabergoline vs placebo/no treatment						
Amir 2015	0	20	1	20	23.5%	0.32 [0.01 , 8.26]
Fetisova 2014	4	65	5	63	76.5%	0.76 [0.19 , 2.97]
Subtotal (95% CI)		**85**		**83**	**100.0%**	**0.66 [0.19 , 2.28]**
Total events:	4		6			
Heterogeneity: Chi² = 0.24, df = 1 (P = 0.63); I² = 0%						
Test for overall effect: Z = 0.66 (P = 0.51)						
Test for subgroup differences: Not applicable						

Analysis 1.7. Comparison 1: Dopamine agonist versus placebo/ no intervention, Outcome 7: Any other adverse events



Study or Subgroup	Dopamine agonist Events	Total	Placebo/no intervention Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.7.1 Cabergoline vs placebo/no treatment						
Alvarez 2007a	8	41	4	41	84.0%	2.24 [0.62 , 8.14]
Subtotal (95% CI)		**41**		**41**	**84.0%**	**2.24 [0.62 , 8.14]**
Total events:	8		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.23 (P = 0.22)						
1.7.2 Quinagolide vs placebo						
Busso 2010 (1)	17	129	0	53	16.0%	16.64 [0.98 , 282.02]
Subtotal (95% CI)		**129**		**53**	**16.0%**	**16.64 [0.98 , 282.02]**
Total events:	17		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.95 (P = 0.05)						
Total (95% CI)		**170**		**94**	**100.0%**	**4.54 [1.49 , 13.84]**
Total events:	25		4			
Heterogeneity: Chi² = 1.96, df = 1 (P = 0.16); I² = 49%						
Test for overall effect: Z = 2.66 (P = 0.008)						
Test for subgroup differences: Chi² = 1.60, df = 1 (P = 0.21), I² = 37.4%						

Footnotes

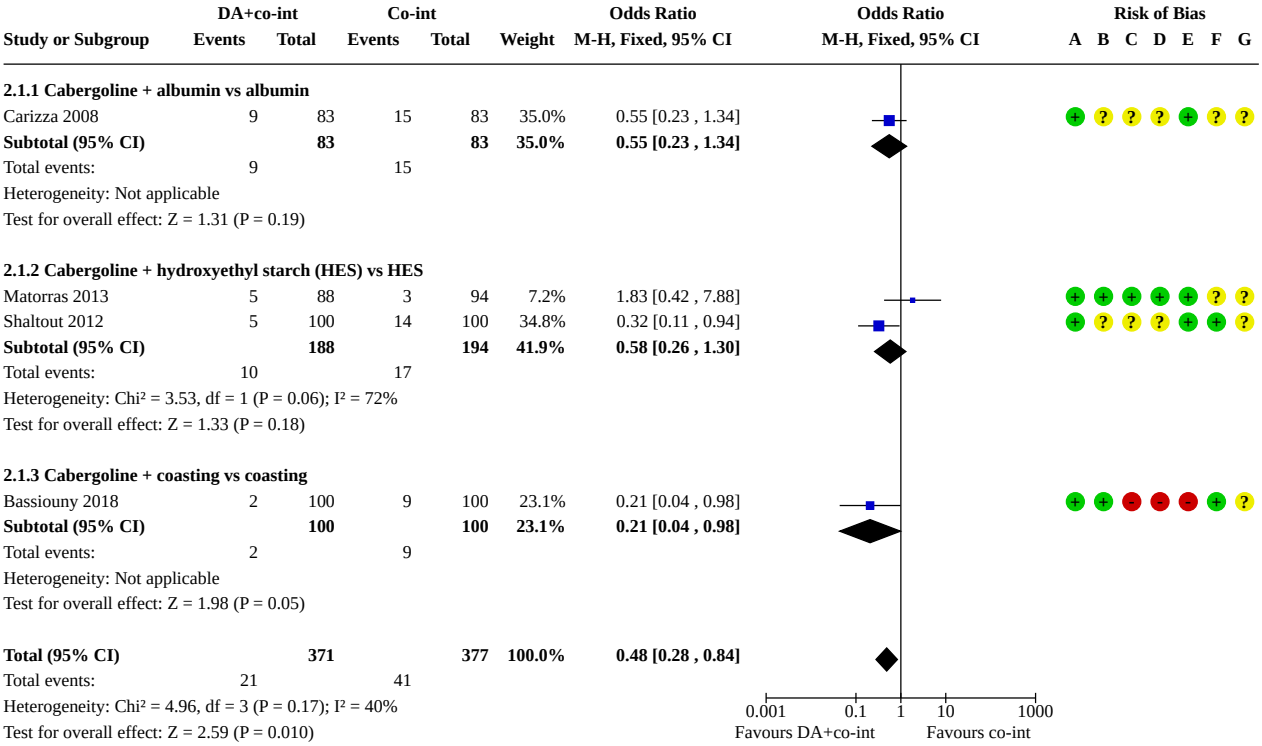
(1) The data were the number of women discontinued because of adverse events.

Comparison 2. Dopamine agonist plus co-intervention (DA+co-int) versus co-intervention (co-int)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Incidence of moderate or severe ovarian hyperstimulation syndrome (OHSS)	4	748	Odds Ratio (M-H, Fixed, 95% CI)	0.48 [0.28, 0.84]
2.1.1 Cabergoline + albumin vs albumin	1	166	Odds Ratio (M-H, Fixed, 95% CI)	0.55 [0.23, 1.34]
2.1.2 Cabergoline + hydroxyethyl starch (HES) vs HES	2	382	Odds Ratio (M-H, Fixed, 95% CI)	0.58 [0.26, 1.30]
2.1.3 Cabergoline + coasting vs coasting	1	200	Odds Ratio (M-H, Fixed, 95% CI)	0.21 [0.04, 0.98]
2.2 Live birth rate	2	400	Odds Ratio (M-H, Fixed, 95% CI)	1.21 [0.81, 1.80]
2.2.1 Cabergoline + HES vs HES	1	200	Odds Ratio (M-H, Fixed, 95% CI)	1.04 [0.59, 1.86]
2.2.2 Cabergoline + coasting vs coasting	1	200	Odds Ratio (M-H, Fixed, 95% CI)	1.38 [0.79, 2.42]
2.3 Clinical pregnancy rate	4	748	Odds Ratio (M-H, Fixed, 95% CI)	1.11 [0.83, 1.49]
2.3.1 Cabergoline + albumin vs albumin	1	166	Odds Ratio (M-H, Fixed, 95% CI)	1.05 [0.56, 1.96]
2.3.2 Cabergoline + HES vs HES	2	382	Odds Ratio (M-H, Fixed, 95% CI)	0.98 [0.65, 1.47]
2.3.3 Cabergoline + coasting vs coasting	1	200	Odds Ratio (M-H, Fixed, 95% CI)	1.49 [0.86, 2.61]
2.4 Multiple pregnancy rate	1	166	Odds Ratio (M-H, Fixed, 95% CI)	2.02 [0.18, 22.77]
2.4.1 Cabergoline + albumin vs albumin	1	166	Odds Ratio (M-H, Fixed, 95% CI)	2.02 [0.18, 22.77]
2.5 Miscarriage rate	3	548	Odds Ratio (M-H, Fixed, 95% CI)	0.65 [0.30, 1.42]
2.5.1 Cabergoline + albumin vs albumin	1	166	Odds Ratio (M-H, Fixed, 95% CI)	0.33 [0.03, 3.19]
2.5.2 Cabergoline + HES vs HES	2	382	Odds Ratio (M-H, Fixed, 95% CI)	0.73 [0.31, 1.68]
2.6 Any other adverse events	2	366	Odds Ratio (M-H, Fixed, 95% CI)	3.03 [0.12, 75.28]
2.6.1 Cabergoline + albumin vs albumin	1	166	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.6.2 Cabergoline + HES vs HES	1	200	Odds Ratio (M-H, Fixed, 95% CI)	3.03 [0.12, 75.28]

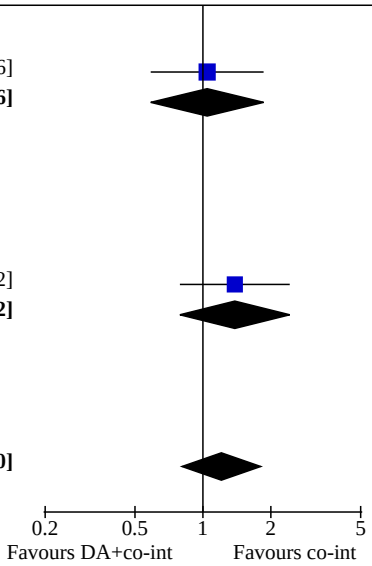
Analysis 2.1. Comparison 2: Dopamine agonist plus co-intervention (DA+co-int) versus co-intervention (co-int), Outcome 1: Incidence of moderate or severe ovarian hyperstimulation syndrome (OHSS)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

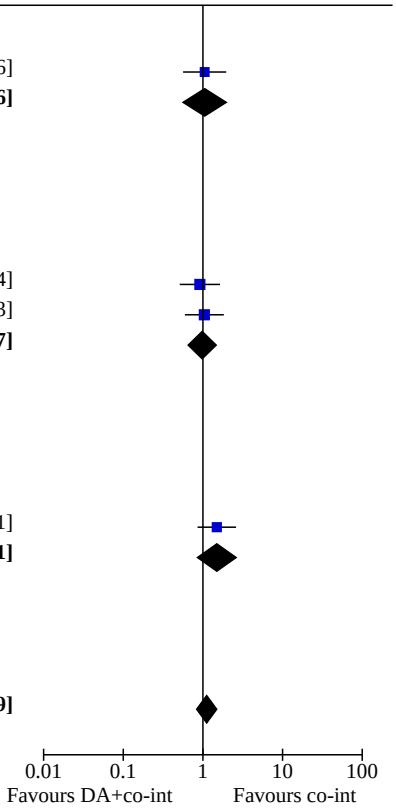
Analysis 2.2. Comparison 2: Dopamine agonist plus co-intervention (DA +co-int) versus co-intervention (co-int), Outcome 2: Live birth rate

Study or Subgroup	DA+co-int Events	DA+co-int Total	Co-int Events	Co-int Total	Weight	Odds Ratio M-H, Fixed, 95% CI
2.2.1 Cabergoline + HES vs HES						
Shaltout 2012	37	100	36	100	52.2%	1.04 [0.59 , 1.86]
Subtotal (95% CI)		**100**		**100**	**52.2%**	**1.04 [0.59 , 1.86]**
Total events:	37		36			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.15 (P = 0.88)						
2.2.2 Cabergoline + coasting vs coasting						
Bassiouny 2018	48	100	40	100	47.8%	1.38 [0.79 , 2.42]
Subtotal (95% CI)		**100**		**100**	**47.8%**	**1.38 [0.79 , 2.42]**
Total events:	48		40			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.14 (P = 0.25)						
Total (95% CI)		**200**		**200**	**100.0%**	**1.21 [0.81 , 1.80]**
Total events:	85		76			
Heterogeneity: Chi² = 0.47, df = 1 (P = 0.49); I² = 0%						
Test for overall effect: Z = 0.92 (P = 0.36)						
Test for subgroup differences: Chi² = 0.47, df = 1 (P = 0.49), I² = 0%						



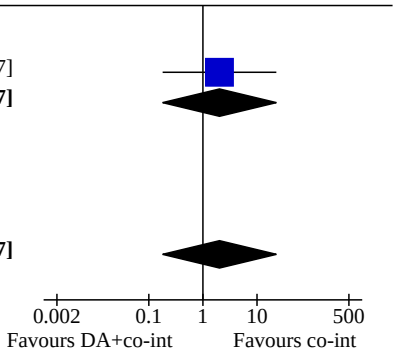
Analysis 2.3. Comparison 2: Dopamine agonist plus co-intervention (DA +co-int) versus co-intervention (co-int), Outcome 3: Clinical pregnancy rate

Study or Subgroup	DA+co-int Events	DA+co-int Total	Co-int Events	Co-int Total	Weight	Odds Ratio M-H, Fixed, 95% CI
2.3.1 Cabergoline + albumin vs albumin						
Carizza 2008	33	83	32	83	22.1%	1.05 [0.56 , 1.96]
Subtotal (95% CI)		**83**		**83**	**22.1%**	**1.05 [0.56 , 1.96]**
Total events:	33		32			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.16 (P = 0.87)						
2.3.2 Cabergoline + HES vs HES						
Matorras 2013	43	88	48	94	27.3%	0.92 [0.51 , 1.64]
Shaltout 2012	42	100	41	100	27.3%	1.04 [0.59 , 1.83]
Subtotal (95% CI)		**188**		**194**	**54.6%**	**0.98 [0.65 , 1.47]**
Total events:	85		89			
Heterogeneity: Chi² = 0.10, df = 1 (P = 0.75); I² = 0%						
Test for overall effect: Z = 0.10 (P = 0.92)						
2.3.3 Cabergoline + coasting vs coasting						
Bassiouny 2018	56	100	46	100	23.3%	1.49 [0.86 , 2.61]
Subtotal (95% CI)		**100**		**100**	**23.3%**	**1.49 [0.86 , 2.61]**
Total events:	56		46			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.41 (P = 0.16)						
Total (95% CI)		**371**		**377**	**100.0%**	**1.11 [0.83 , 1.49]**
Total events:	174		167			
Heterogeneity: Chi² = 1.59, df = 3 (P = 0.66); I² = 0%						
Test for overall effect: Z = 0.74 (P = 0.46)						
Test for subgroup differences: Chi² = 1.49, df = 2 (P = 0.47), I² = 0%						



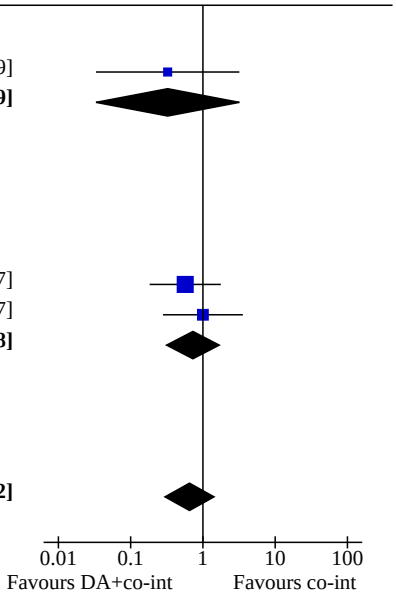
Analysis 2.4. Comparison 2: Dopamine agonist plus co-intervention (DA +co-int) versus co-intervention (co-int), Outcome 4: Multiple pregnancy rate

Study or Subgroup	DA+co-int Events	DA+co-int Total	Co-int Events	Co-int Total	Weight	Odds Ratio M-H, Fixed, 95% CI
2.4.1 Cabergoline + albumin vs albumin						
Carizza 2008	2	83	1	83	100.0%	2.02 [0.18 , 22.77]
Subtotal (95% CI)		**83**		**83**	**100.0%**	**2.02 [0.18 , 22.77]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.57 (P = 0.57)						
Total (95% CI)		**83**		**83**	**100.0%**	**2.02 [0.18 , 22.77]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.57 (P = 0.57)						
Test for subgroup differences: Not applicable						



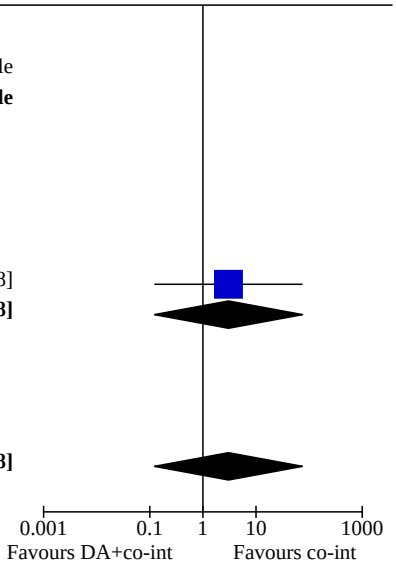
Analysis 2.5. Comparison 2: Dopamine agonist plus co-intervention (DA +co-int) versus co-intervention (co-int), Outcome 5: Miscarriage rate

Study or Subgroup	DA+co-int Events	DA+co-int Total	Co-int Events	Co-int Total	Weight	Odds Ratio M-H, Fixed, 95% CI
2.5.1 Cabergoline + albumin vs albumin						
Carizza 2008	1	83	3	83	18.6%	0.33 [0.03 , 3.19]
Subtotal (95% CI)		**83**		**83**	**18.6%**	**0.33 [0.03 , 3.19]**
Total events:	1		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.96 (P = 0.34)						
2.5.2 Cabergoline + HES vs HES						
Matorras 2013	5	88	9	94	51.6%	0.57 [0.18 , 1.77]
Shaltout 2012	5	100	5	100	29.8%	1.00 [0.28 , 3.57]
Subtotal (95% CI)		**188**		**194**	**81.4%**	**0.73 [0.31 , 1.68]**
Total events:	10		14			
Heterogeneity: Chi² = 0.42, df = 1 (P = 0.52); I² = 0%						
Test for overall effect: Z = 0.75 (P = 0.46)						
Total (95% CI)		**271**		**277**	**100.0%**	**0.65 [0.30 , 1.42]**
Total events:	11		17			
Heterogeneity: Chi² = 0.85, df = 2 (P = 0.66); I² = 0%						
Test for overall effect: Z = 1.07 (P = 0.28)						
Test for subgroup differences: Chi² = 0.42, df = 1 (P = 0.52), I² = 0%						



Analysis 2.6. Comparison 2: Dopamine agonist plus co-intervention (DA+co-int) versus co-intervention (co-int), Outcome 6: Any other adverse events

Study or Subgroup	DA+co-int Events	DA+co-int Total	Co-int Events	Co-int Total	Weight	Odds Ratio M-H, Fixed, 95% CI
2.6.1 Cabergoline + albumin vs albumin						
Carizza 2008	0	83	0	83		Not estimable
Subtotal (95% CI)		**83**		**83**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.6.2 Cabergoline + HES vs HES						
Shaltout 2012	1	100	0	100	100.0%	3.03 [0.12 , 75.28]
Subtotal (95% CI)		**100**		**100**	**100.0%**	**3.03 [0.12 , 75.28]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
Total (95% CI)		**183**		**183**	**100.0%**	**3.03 [0.12 , 75.28]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
Test for subgroup differences: Not applicable						



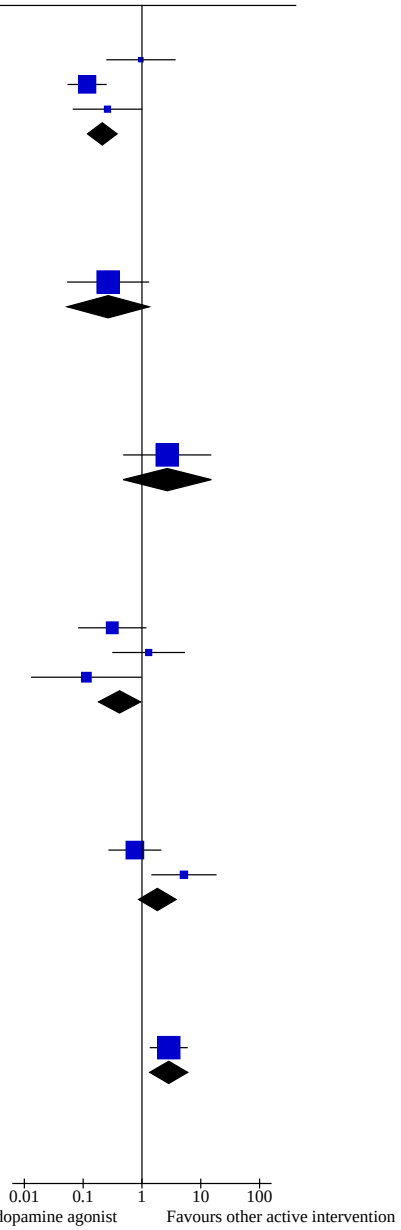
Comparison 3. Dopamine agonist versus other active interventions

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Incidence of moderate or severe ovarian hyperstimulation syndrome (OHSS)	10		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1.1 Cabergoline vs human albumin	3	296	Odds Ratio (M-H, Fixed, 95% CI)	0.21 [0.12, 0.38]
3.1.2 Cabergoline vs prednisolone	1	150	Odds Ratio (M-H, Fixed, 95% CI)	0.27 [0.05, 1.33]
3.1.3 Cabergoline vs hydroxyethyl starch (HES)	1	61	Odds Ratio (M-H, Fixed, 95% CI)	2.69 [0.48, 15.10]
3.1.4 Cabergoline vs coasting	3	320	Odds Ratio (M-H, Fixed, 95% CI)	0.42 [0.18, 0.95]
3.1.5 Cabergoline vs calcium infusion	2	400	Odds Ratio (M-H, Fixed, 95% CI)	1.83 [0.88, 3.81]
3.1.6 Cabergoline vs diosmin	1	200	Odds Ratio (M-H, Fixed, 95% CI)	2.85 [1.35, 6.00]
3.2 Live birth rate	2	430	Odds Ratio (M-H, Fixed, 95% CI)	1.08 [0.73, 1.59]
3.2.1 Cabergoline vs coasting	1	200	Odds Ratio (M-H, Fixed, 95% CI)	1.04 [0.59, 1.83]
3.2.2 Cabergoline vs calcium infusion	1	230	Odds Ratio (M-H, Fixed, 95% CI)	1.11 [0.66, 1.89]
3.3 Clinical pregnancy rate	7	1060	Odds Ratio (M-H, Fixed, 95% CI)	1.04 [0.81, 1.33]
3.3.1 Cabergoline vs human albumin	1	140	Odds Ratio (M-H, Fixed, 95% CI)	0.68 [0.33, 1.38]
3.3.2 Cabergoline vs coasting	3	320	Odds Ratio (M-H, Fixed, 95% CI)	1.46 [0.92, 2.32]
3.3.3 Cabergoline vs calcium infusion	2	400	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.67, 1.49]
3.3.4 Cabergoline vs diosmin	1	200	Odds Ratio (M-H, Fixed, 95% CI)	0.89 [0.51, 1.55]
3.4 Multiple pregnancy rate	3	400	Odds Ratio (M-H, Fixed, 95% CI)	0.87 [0.47, 1.59]
3.4.1 Cabergoline vs human albumin	1	140	Odds Ratio (M-H, Fixed, 95% CI)	0.58 [0.13, 2.54]
3.4.2 Cabergoline vs coasting	1	60	Odds Ratio (M-H, Fixed, 95% CI)	5.35 [0.25, 116.31]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.4.3 Cabergoline vs diosmin	1	200	Odds Ratio (M-H, Fixed, 95% CI)	0.83 [0.41, 1.67]
3.5 Miscarriage rate	4	630	Odds Ratio (M-H, Fixed, 95% CI)	0.66 [0.35, 1.25]
3.5.1 Cabergoline vs human albumin	1	140	Odds Ratio (M-H, Fixed, 95% CI)	0.32 [0.03, 3.19]
3.5.2 Cabergoline vs coasting	1	60	Odds Ratio (M-H, Fixed, 95% CI)	0.19 [0.01, 4.06]
3.5.3 Cabergoline vs calcium infusion	1	230	Odds Ratio (M-H, Fixed, 95% CI)	0.63 [0.27, 1.48]
3.5.4 Cabergoline vs diosmin	1	200	Odds Ratio (M-H, Fixed, 95% CI)	1.21 [0.36, 4.11]
3.6 Any other adverse events	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.6.1 Cabergoline vs calcium infusion	1	170	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable

Analysis 3.1. Comparison 3: Dopamine agonist versus other active interventions, Outcome 1: Incidence of moderate or severe ovarian hyperstimulation syndrome (OHSS)

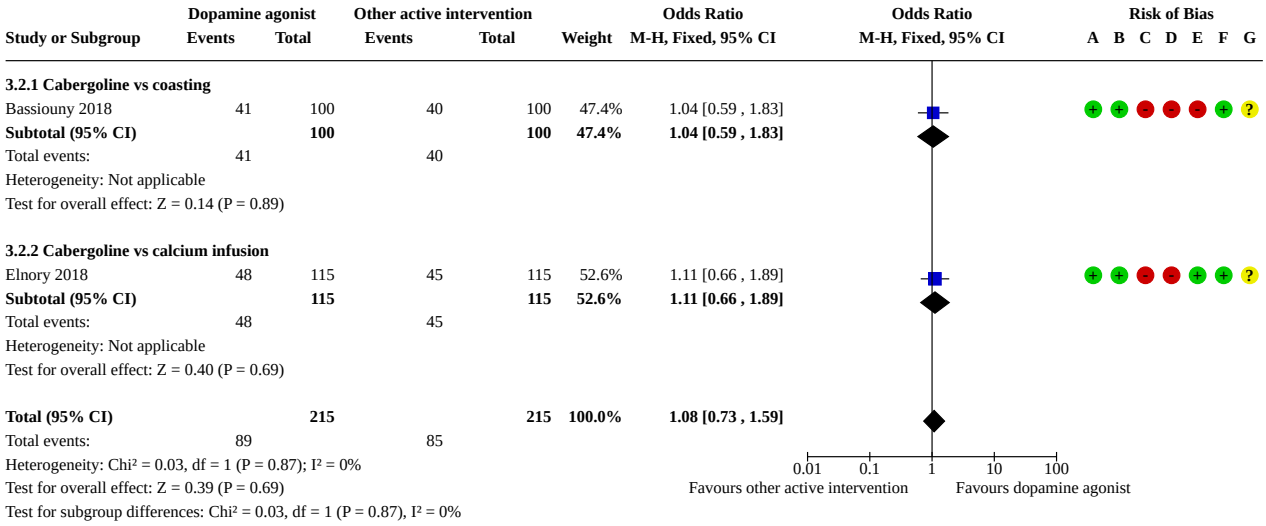
Study or Subgroup	Dopamine agonist Events	Total	Other active intervention Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
3.1.1 Cabergoline vs human albumin						
Ghahiri 2015	5	31	5	30	8.2%	0.96 [0.25 , 3.73]
Tehraninejad 2012	15	70	49	70	74.0%	0.12 [0.05 , 0.25]
Torabizadeh 2013	3	47	10	48	17.8%	0.26 [0.07 , 1.01]
Subtotal (95% CI)		**148**		**148**	**100.0%**	**0.21 [0.12 , 0.38]**
Total events:	23		64			
Heterogeneity: Chi² = 7.18, df = 2 (P = 0.03); I² = 72%						
Test for overall effect: Z = 5.24 (P < 0.00001)						
3.1.2 Cabergoline vs prednisolone						
Salah 2012	2	75	7	75	100.0%	0.27 [0.05 , 1.33]
Subtotal (95% CI)		**75**		**75**	**100.0%**	**0.27 [0.05 , 1.33]**
Total events:	2		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.62 (P = 0.11)						
3.1.3 Cabergoline vs hydroxyethyl starch (HES)						
Ghahiri 2015	5	31	2	30	100.0%	2.69 [0.48 , 15.10]
Subtotal (95% CI)		**31**		**30**	**100.0%**	**2.69 [0.48 , 15.10]**
Total events:	5		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.13 (P = 0.26)						
3.1.4 Cabergoline vs coasting						
Bassiouny 2018	3	100	9	100	46.4%	0.31 [0.08 , 1.19]
Dalal 2014 (1)	5	30	4	30	17.7%	1.30 [0.31 , 5.40]
Sohrabvand 2009	1	30	7	30	35.9%	0.11 [0.01 , 0.99]
Subtotal (95% CI)		**160**		**160**	**100.0%**	**0.42 [0.18 , 0.95]**
Total events:	9		20			
Heterogeneity: Chi² = 4.02, df = 2 (P = 0.13); I² = 50%						
Test for overall effect: Z = 2.09 (P = 0.04)						
3.1.5 Cabergoline vs calcium infusion						
El-Shaer 2019	7	85	9	85	75.8%	0.76 [0.27 , 2.14]
Elnory 2018	14	115	3	115	24.2%	5.17 [1.45 , 18.53]
Subtotal (95% CI)		**200**		**200**	**100.0%**	**1.83 [0.88 , 3.81]**
Total events:	21		12			
Heterogeneity: Chi² = 5.32, df = 1 (P = 0.02); I² = 81%						
Test for overall effect: Z = 1.61 (P = 0.11)						
3.1.6 Cabergoline vs diosmin						
Saad 2017	28	100	12	100	100.0%	2.85 [1.35 , 6.00]
Subtotal (95% CI)		**100**		**100**	**100.0%**	**2.85 [1.35 , 6.00]**
Total events:	28		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.76 (P = 0.006)						



Footnotes

(1) Both groups also received a background treatment of HES.

Analysis 3.2. Comparison 3: Dopamine agonist versus other active interventions, Outcome 2: Live birth rate

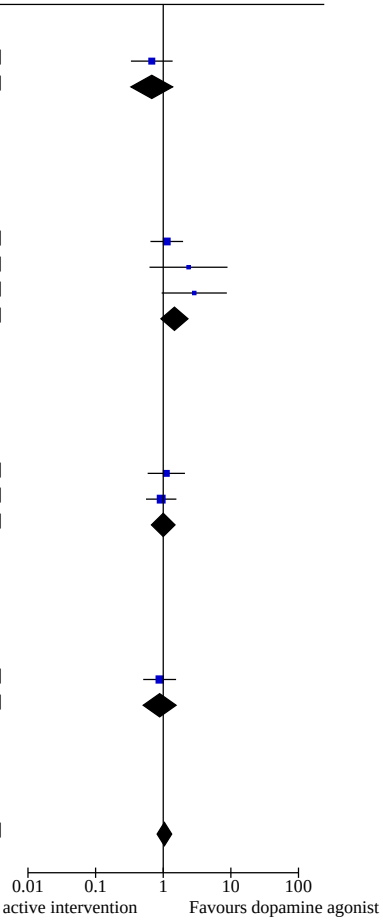


Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 3.3. Comparison 3: Dopamine agonist versus other active interventions, Outcome 3: Clinical pregnancy rate

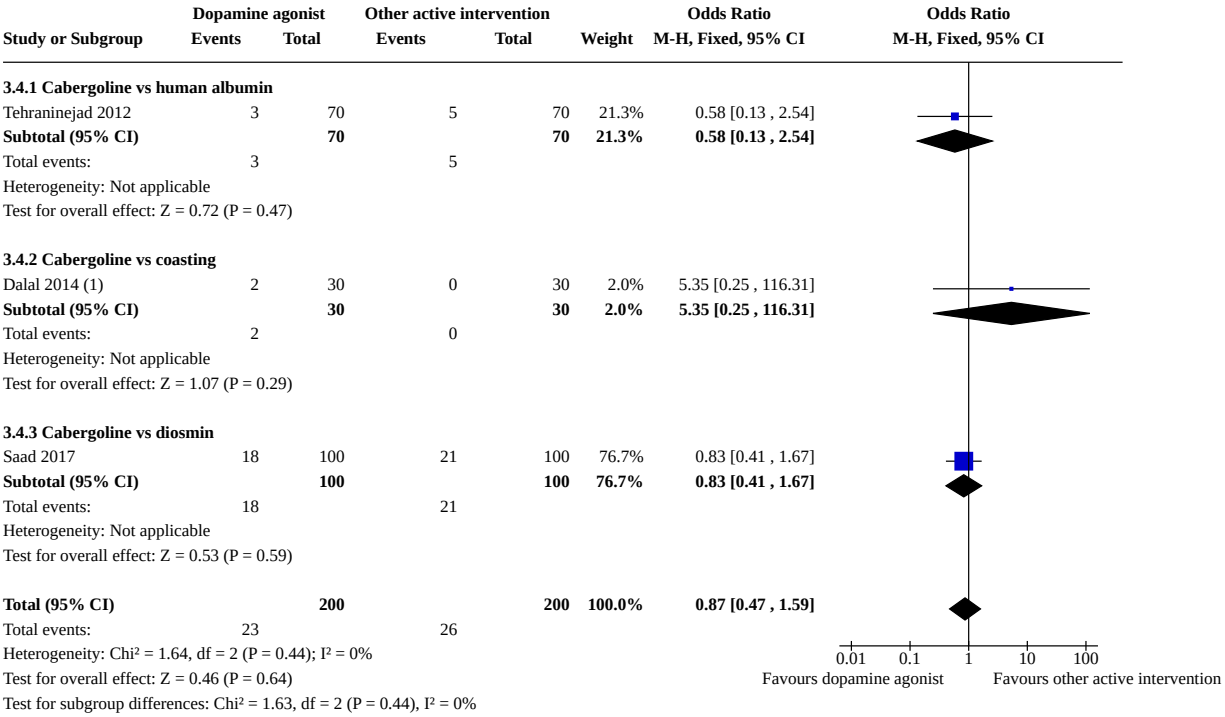
Study or Subgroup	Dopamine agonist Events	Total	Other active intervention Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
3.3.1 Cabergoline vs human albumin						
Tehraninejad 2012	20	70	26	70	15.1%	0.68 [0.33 , 1.38]
Subtotal (95% CI)		**70**		**70**	**15.1%**	**0.68 [0.33 , 1.38]**
Total events:	20		26			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.08 (P = 0.28)						
3.3.2 Cabergoline vs coasting						
Bassiouny 2018	49	100	46	100	19.1%	1.13 [0.65 , 1.97]
Dalal 2014 (1)	8	30	4	30	2.4%	2.36 [0.63 , 8.92]
Sohrabvand 2009	14	30	7	30	3.0%	2.88 [0.95 , 8.72]
Subtotal (95% CI)		**160**		**160**	**24.6%**	**1.46 [0.92 , 2.32]**
Total events:	71		57			
Heterogeneity: Chi² = 2.77, df = 2 (P = 0.25); I² = 28%						
Test for overall effect: Z = 1.63 (P = 0.10)						
3.3.3 Cabergoline vs calcium infusion						
El-Shaer 2019	30	85	28	85	14.8%	1.11 [0.59 , 2.09]
Elnory 2018	58	115	60	115	24.2%	0.93 [0.56 , 1.56]
Subtotal (95% CI)		**200**		**200**	**39.0%**	**1.00 [0.67 , 1.49]**
Total events:	88		88			
Heterogeneity: Chi² = 0.17, df = 1 (P = 0.68); I² = 0%						
Test for overall effect: Z = 0.00 (P = 1.00)						
3.3.4 Cabergoline vs diosmin						
Saad 2017	55	100	58	100	21.3%	0.89 [0.51 , 1.55]
Subtotal (95% CI)		**100**		**100**	**21.3%**	**0.89 [0.51 , 1.55]**
Total events:	55		58			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.43 (P = 0.67)						
Total (95% CI)		**530**		**530**	**100.0%**	**1.04 [0.81 , 1.33]**
Total events:	234		229			
Heterogeneity: Chi² = 6.72, df = 6 (P = 0.35); I² = 11%						
Test for overall effect: Z = 0.32 (P = 0.75)						
Test for subgroup differences: Chi² = 3.89, df = 3 (P = 0.27), I² = 23.0%						



Footnotes

(1) Both groups also received a background treatment of HES.

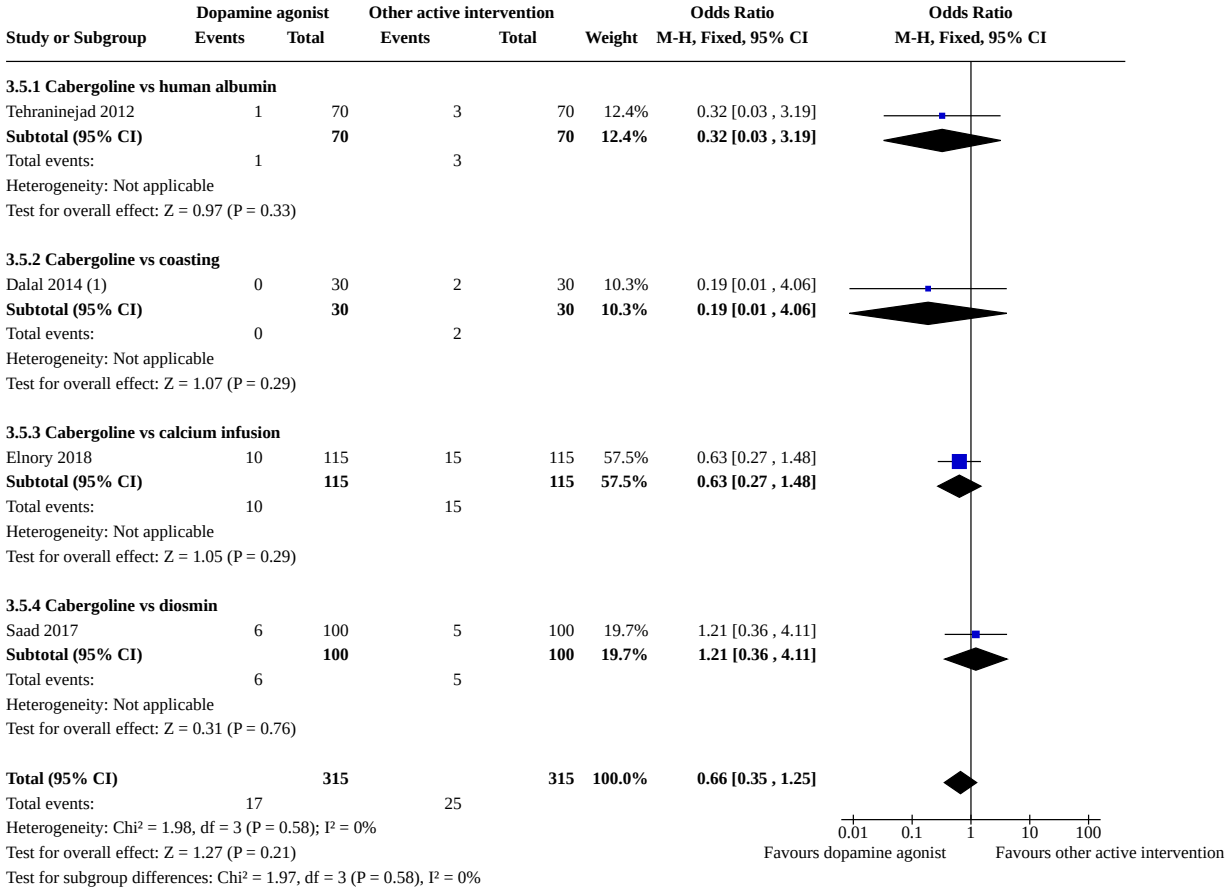
Analysis 3.4. Comparison 3: Dopamine agonist versus other active interventions, Outcome 4: Multiple pregnancy rate



Footnotes

(1) Both groups also received a background treatment of HES.

Analysis 3.5. Comparison 3: Dopamine agonist versus other active interventions, Outcome 5: Miscarriage rate

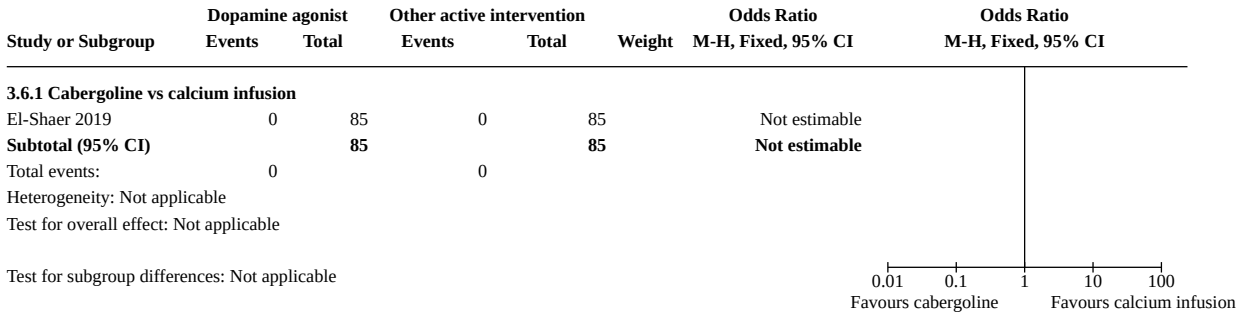


Study or Subgroup	Dopamine agonist Events	Total	Other active intervention Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
3.5.1 Cabergoline vs human albumin						
Tehraninejad 2012	1	70	3	70	12.4%	0.32 [0.03 , 3.19]
Subtotal (95% CI)		**70**		**70**	**12.4%**	**0.32 [0.03 , 3.19]**
Total events:	1		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.97 (P = 0.33)						
3.5.2 Cabergoline vs coasting						
Dalal 2014 (1)	0	30	2	30	10.3%	0.19 [0.01 , 4.06]
Subtotal (95% CI)		**30**		**30**	**10.3%**	**0.19 [0.01 , 4.06]**
Total events:	0		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.07 (P = 0.29)						
3.5.3 Cabergoline vs calcium infusion						
Elnory 2018	10	115	15	115	57.5%	0.63 [0.27 , 1.48]
Subtotal (95% CI)		**115**		**115**	**57.5%**	**0.63 [0.27 , 1.48]**
Total events:	10		15			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.05 (P = 0.29)						
3.5.4 Cabergoline vs diosmin						
Saad 2017	6	100	5	100	19.7%	1.21 [0.36 , 4.11]
Subtotal (95% CI)		**100**		**100**	**19.7%**	**1.21 [0.36 , 4.11]**
Total events:	6		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.31 (P = 0.76)						
Total (95% CI)		**315**		**315**	**100.0%**	**0.66 [0.35 , 1.25]**
Total events:	17		25			
Heterogeneity: Chi² = 1.98, df = 3 (P = 0.58); I² = 0%						
Test for overall effect: Z = 1.27 (P = 0.21)						
Test for subgroup differences: Chi² = 1.97, df = 3 (P = 0.58), I² = 0%						

Footnotes

(1) Both groups also received a background treatment of HES.

Analysis 3.6. Comparison 3: Dopamine agonist versus other active interventions, Outcome 6: Any other adverse events



Study or Subgroup	Dopamine agonist Events	Total	Other active intervention Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
3.6.1 Cabergoline vs calcium infusion						
El-Shaer 2019	0	85	0	85		Not estimable
Subtotal (95% CI)		**85**		**85**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						

APPENDICES

Appendix 1. The Cochrane Gynaecology and Fertility Group specialised register search strategy

Procite Platform

Searched 4 May 2020

Keywords CONTAINS "ovarian hyperstimulation syndrome "or "ovarian hyperstimulation" or "OHSS" or Title CONTAINS "ovarian hyperstimulation syndrome " or "ovarian hyperstimulation" or "OHSS"

AND

Keywords CONTAINS "cabergoline" or "Dopamine agonists" or "Dopamine" or "bromocriptine" or "quinagolide" or Title CONTAINS "cabergoline" or "Dopamine agonists" or "Dopamine" or "bromocriptine" or "quinagolide"

50 records

Appendix 2. CENTRAL via the Cochrane Register of Studies Online (CRSO) search strategy

CRSO Web platform

Searched 4 May 2020

#1 MESH DESCRIPTOR Ovarian Hyperstimulation Syndrome EXPLODE ALL TREES 256

#2 OHSS:TI,AB,KY 656

#3 (Ovar* adj2 Hyperstimulation):TI,AB,KY 1612

#4 #1 OR #2 OR #3 1757

#5 MESH DESCRIPTOR Ergolines EXPLODE ALL TREES 1030

#6 Ergoline*:TI,AB,KY 254

#7 cabergoline:TI,AB,KY 301

#8 (Dostinex or Cabaser*):TI,AB,KY 20

#9 (Dopamine Agonist*):TI,AB,KY 1261

#10 MESH DESCRIPTOR Dopamine Agonists EXPLODE ALL TREES 1631

#11 MESH DESCRIPTOR Bromocriptine EXPLODE ALL TREES 492

#12 Bromocriptine:TI,AB,KY 931

#13 quinagolide*:TI,AB,KY 26

#14 #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 3049

#15 #4 AND #14 82

Appendix 3. MEDLINE search strategy

Ovid platform

Searched from 1946 to 4 May 2020

1 exp Ovarian Hyperstimulation Syndrome/ (2247)
2 OHSS.tw. (1743)
3 (Ovar$ adj2 Hyperstimulation).tw. (5074)
4 or/1-3 (5569)
5 exp Ergolines/ (21308)
6 cabergoline.tw. (1515)
7 Ergoline$.tw. (568)
8 (Dostinex or Cabaser$).tw. (16)
9 Dopamine Agonist$.tw. (7587)
10 exp Dopamine Agonists/ (31994)
11 exp Bromocriptine/ (6953)
12 Bromocriptine.tw. (6809)
13 quinagolide$.tw. (130)
14 or/5-13 (47436)

15 4 and 14 (126)
16 randomized controlled trial.pt. (504846)
17 controlled clinical trial.pt. (93651)
18 randomized.ab. (477493)
19 placebo.tw. (212896)
20 clinical trials as topic.sh. (190976)
21 randomly.ab. (332008)
22 trial.ti. (217172)
23 (crossover or cross-over or cross over).tw. (84381)
24 or/16-23 (1314738)
25 (animals not (humans and animals)).sh. (4661834)
26 24 not 25 (1208420)
27 26 and 15 (43)

Appendix 4. Embase search strategy

Ovid platform

Searched from 1980 to 4 May 2020
1 exp ovary hyperstimulation/ (9411)
2 (ovar$ adj2 hyperstimulation).tw. (7433)
3 OHSS.tw. (2992)
4 or/1-3 (11394)
5 cabergoline.tw. (2346)
6 exp ergoline derivative/ (739)
7 ergoline$.tw. (647)
8 (Dostinex or Cabaser$).tw. (370)
9 exp dopamine receptor stimulating agent/ or exp cabergoline/ (191920)
10 (dopamine adj2 agent$).tw. (573)
11 (dopamine adj2 agonist$).tw. (13731)
12 quinagolide$.tw. (192)
13 exp bromocriptine/ (18487)
14 bromocriptine.tw. (7507)
15 or/5-14 (194126)
16 Clinical Trial/ (963610)
17 Randomized Controlled Trial/ (597076)
18 exp randomization/ (86768)
19 Single Blind Procedure/ (38692)
20 Double Blind Procedure/ (168832)
21 Crossover Procedure/ (62819)
22 Placebo/ (335555)
23 Randomi?ed controlled trial$.tw. (226140)
24 Rct.tw. (36646)
25 random allocation.tw. (2000)
26 randomly allocated.tw. (34759)
27 allocated randomly.tw. (2530)
28 (allocated adj2 random).tw. (812)
29 Single blind$.tw. (24445)
30 Double blind$.tw. (201171)
31 ((treble or triple) adj blind$).tw. (1132)
32 placebo$.tw. (300426)
33 prospective study/ (595141)
34 or/16-33 (2170980)
35 case study/ (68239)
36 case report.tw. (398561)
37 abstract report/ or letter/ (1092750)
38 or/35-37 (1549189)
39 34 not 38 (2117772)
40 4 and 15 and 39 (124)

Appendix 5. PsycINFO search strategy

Ovid platform

Searched from 1806 to 4 May 2020

1 Ovarian Hyperstimulation Syndrome.tw. (6)
2 OHSS.tw. (8)
3 (Ovar$ adj2 Hyperstimulation).tw. (13)
4 or/1-3 (19)
5 exp dopamine agonists/ (23857)
6 cabergoline.tw. (134)
7 Ergoline$.tw. (48)
8 (Dostinex or Cabaser$).tw. (2)
9 Dopamine Agonist$.tw. (2602)
10 Bromocriptine.tw. (708)
11 exp bromocriptine/ (302)
12 quinagolide$.tw. (6)
13 or/5-12 (25446)
14 4 and 13 (0)

Appendix 6. CINAHL search strategy

EBSCO platform

Searched from 1961 to 4 May 2020

#	Query	Results
S14	S4 AND S13	33
S13	S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12	2964
S12	TX quinagolide*	11
S11	TX Bromocriptine	551
S10	(MM "Bromocriptine")	185
S9	TX (Dostinex or Cabaser*)	6
S8	TX cabergoline	220
S7	TX Dopamine Agonist*	2361
S6	(MM "Dopamine Agonists+")	1202
S5	TX Ergoline*	22
S4	S1 OR S2 OR S3	1007
S3	TX (Ovar* N2 Hyperstimulation)	960
S2	TX OHSS	286
S1	(MM "Ovarian Hyperstimulation Syndrome")	343

Appendix 7. Data extraction form

General trial characteristics

First author

Publish year

Citation:

Contact author detail:

Eligibility

1. Is the study an RCT?

2. High-risk women?

3. How OHSS defined?

4. Administration of cabergoline?

Decision: if all replies yes means include, otherwise exclude

Characteristics of the included studies

Risk of bias

1. sequence generation (low, high or unclear)
2. allocation concealment (low, high or unclear)
3. blinding of participants (low, high or unclear)
4. personnel and outcome assessors (low, high or unclear)
5. incomplete outcome data, and selective outcome reporting (low, high or unclear)

Methods

Inclusion criteria:

Exclusion criteria:

Participants

Total number:

Diagnosis criteria:

Age (mean ± SD): treat group vs control group:

BMI (mean ± SD): treat group vs control group:

Duration of infertility:

Causes of infertility:

Interventions

Treat group:(dose, administration of drug, duration of treatment)

Control group (placebo or no intervention):

Outcomes

1. Incidence of moderate and / or severe OHSS

(Continued)

2. Incidence of early and / or late OHSS
3. Live Birth rate
4. Any other adverse effects of the treatment
5. Miscarriage rate
6. Implantation rate
7. Clinical pregnancy rate
8. Multiple pregnancy rate

Results

- Number of participants allocated to each intervention group.

For each outcome of interest:

- Sample size.
- Missing participants*.
- Summary data for each intervention group (e.g. 2×2 table for dichotomous data).
- [Estimate of effect with confidence interval; P value].
- [Subgroup analyses].

Miscellaneous

- Funding source.
- Key conclusions of the study authors.
- Miscellaneous comments from the study authors.
- References to other relevant studies.
- Correspondence required.
- Miscellaneous comments by the review authors.

BMI: body mass index; **OHSS:** ovarian hyperstimulation syndrome; **RCT:** randomised controlled trial; **SD:** standard deviation.

WHAT'S NEW

Date	Event	Description
4 May 2020	New search has been performed	In this update, we included 6 new trials (Bassiouny 2018; El-Shaer 2019; Elnory 2018; Kilic 2015; Saad 2017; Singh 2017). Results, GRADE, and references updated.
4 May 2020	New citation required but conclusions have not changed	The addition of 6 new trials has not led to a change in the conclusions of this review.

HISTORY

Protocol first published: Issue 7, 2010
Review first published: Issue 2, 2012

Date	Event	Description
21 August 2016	New citation required and conclusions have changed	The extended scope and addition of 14 studies have led to a change in the conclusions of this review.
21 August 2016	New search has been performed	Amended title and methods to include all kinds of dopamine agonist, new searches, included 14 studies (Alhalabi 2011; Amir 2015; Beltrame 2013; Busso 2010; Dalal 2014; Fetisova 2014; Ghahiri 2015; Jellad 2017, Matorras 2013; Salah 2012; Shaltout 2012; Sohrabvand 2009; Tehraninejad 2012; Torabizadeh 2013).
24 April 2013	New search has been performed	Review Update, more data extracted from Shaltout 2012
17 December 2012	New citation required but conclusions have not changed	Three new trials added, but no change to conclusions
17 December 2012	New search has been performed	Review updated, three trials added: Salah 2012; Shaltout 2012; Tehraninejad 2012
4 September 2011	New search has been performed	Search updated to 2 September 2011; substantive amendment
10 January 2010	Amended	Converted to new review format.
2 January 2010	New citation required and major changes	Substantive amendment

CONTRIBUTIONS OF AUTHORS

HT: proposed the original title, selected studies, extracted data, assessed studies, analysed and interpreted the data, prepared and revised the review.

SM: proposed the 2016 title change and update, selected studies, extracted data, assessed studies, interpreted data, prepared and revised the review.

AW: checked the data and revised the review.

SZ: read and commented on the draft review.

RH: read and commented on the draft review.

DECLARATIONS OF INTEREST

HT: none.

SM: none.

AW: none.

SZ: none.

RH is the Medical Director of Fertility Specialists of Western Australia, has equity interests in and is on the Board of Western IVF, is on the Medical Advisory Boards of MSD, Merck-Serono and Ferring Pharmaceuticals and in the last two years has received educational grant support from Ferring Pharmaceuticals and in the last five years (other than the last year) has also received travel and accommodation from MSD and Merck Serono.

SOURCES OF SUPPORT

Internal sources

- Peking University Third Hospital, China

  Peking University Third Hospital
- King Edward Memorial Hospital, Australia, Australia

  King Edward Memorial Hospital
- The University of Western Australia, King Edward Memorial Hospital and Fertility Specialists of Western Australia, Australia

  The University of Western Australia, King Edward Memorial Hospital and Fertility Specialists of Western Australia

External sources

- none, UK

  There were no external sources of support for this review

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

2016 update: we amended the protocol to broaden the scope of the review from "cabergoline" to "dopamine agonists" as the studied intervention. We changed the search strategies, inclusion criteria, and title of the review accordingly.

Methods: changed review authors for selection of studies or data extraction and management.

Subgroups: added subgroups by type of dopamine agonist.

Sensitivity analysis: added sensitivity analyses by excluding trials with high risk of bias and by using a random-effects model.

Subgroup analysis on route of administration of drugs could not be performed as all dopamine agonists were administered orally.

Subgroup analysis on number of embryos transferred could not be performed as the RCTs did not provide these data.

Subgroup analyses on duration of treatment were not performed due to varied duration among the trials, which might result in only one included trial.

Aihua Wang joined the review team.

INDEX TERMS

Medical Subject Headings (MeSH)

Abortion, Spontaneous [prevention & control]; Administration, Oral; Aminoquinolines [therapeutic use]; Bromocriptine [therapeutic use]; Cabergoline [therapeutic use]; Dopamine Agonists [administration & dosage] [*therapeutic use]; Ergolines [therapeutic use]; *Fertilization in Vitro; Live Birth [epidemiology]; Ovarian Hyperstimulation Syndrome [epidemiology] [*prevention & control]; Placebos [therapeutic use]; Pregnancy Rate; Randomized Controlled Trials as Topic; Sperm Injections, Intracytoplasmic

MeSH check words

Female; Humans; Pregnancy